BARKER (L.F.)

A STUDY OF SOME FATAL CASES OF MALARIA.

BY

LEWELLYS F. BARKER, M. B., TOR.,

Associate in Anatomy, Johns Hopkins University, and Assistant Resident Pathologist, The Johns Hopkins Hospital.

Reprinted from *The Johns Hopkins Hospital Reports*, Vol. V, 1895.

BALTIMORE
THE JOHNS HOPKINS PRESS
1895

A STUDY OF SOME FATAL CASES OF MALARIA.

BY

LEWELLYS F. BARKER, M. B., TOR.,

Associate in Anatomy, Johns Hopkins University, and Assistant Resident Pathologist, The Johns Hopkins Hospital.

Reprinted from *The Johns Hopkins Hospital Reports*, Vol. V, 1895.

BALTIMORE
THE JOHNS HOPKINS PRESS
1895

JOHN MURPHY & CO., PRINTERS,
BALTIMORE.

A STUDY OF SOME FATAL CASES OF MALARIA.

By LEWELLYS F. BARKER, M. B., Tor.,
Associate in Anatomy and Assistant Resident Pathologist.

I.

INTRODUCTION.

The material for the following study was derived from the bodies of patients coming to autopsy in the Pathological Laboratory of the Johns Hopkins University and Hospital between 1889 and 1894.

For the permission to study the tissues and to extract protocols from the post-mortem records I have to thank Professor W. H. Welch; the clinical histories of the cases have been put into my hands through the courtesy of Professor William Osler.

Since the discovery of Laveran's parasite which rendered possible under ordinary circumstances the early recognition of a malarial infection by means of the microscopical examination of the fresh blood, it has become a comparatively rare occurrence for a patient to die of this disease. The study of the pathology of malaria is consequently limited to the few instances in which the patients die from traumatism or from some inter-current disease, and to those rare cases of pernicious malarial infection which terminate fatally.

The tissues from the cases referred to in this paper were hardened some in alcohol, some in Müller's fluid, and others in Flemming's solution. For general study the tissues fixed in strong alcohol served best, while for the investigation of certain points those fixed in Flemming's solution gave excellent results, those preserved in Müller's fluid being the least satisfactory. The tissues were imbedded in celloidin and in paraffin. For staining haematoxylin and eosin, alum-cochineal, safranin, gentian violet, aqueous magenta, Weigert's fibrin-stain and the triple stain (Ehrlich-Biondi) were employed, while for the study of the pigments and of the iron-containing compounds derived from the red blood corpuscles certain sections were treated with ammonium sulphide and others with hydrochloric acid and ferrocyanide of potassium[1] (method of Perls).

[1] Concerning the reactions for iron and the unsatisfactory nomenclature of iron-containing compounds, cf. article by J. J. Abel, Virch. arch., Bd. 120, p. 204; also articles by A. B. Macallum, Proc. Roy. Soc., &c.

In order to determine accurately the relation of the parasites and pigments to the tissues many sections both stained and unstained were examined in media of different refractive power. For this purpose water, glycerine, balsam, a saturated solution of acetate of potassium, Farrant's medium, and solutions of chloral-hydrate were employed.

The enormous strides made in late years in the clinical studies of malaria has rendered a re-working of the pathology highly desirable. The majority of the investigators have contented themselves with the study of the blood taken from the peripheral circulation, or from that obtained from tappings of the spleen made during life. Some however, among them Bignami, Marchiafava, Guarnieri and Golgi in Italy, Metschnikoff, Laveran, Kelsch and Kiener in France, and Osler, Councilman, Abbott and Dock in America have made contributions to our knowledge of the pathology of the affection as it concerns the internal organs of the body.

In this report will be found the clinical histories of four cases of malaria, in three of which the parasites were of the aestivo-autumnal and in one of which they were of the tertian type, together with a description of the pathological findings in each. As an appendix are added certain observations dealing with the unequal distribution of the parasites in the body, and with phagocytosis in malaria.

II.

CASE A.—*Aestivo-autumnal malaria; anomalous symptoms during life.*

L. K., aet. 81, was admitted to Prof. Osler's wards July 18, 1889, complaining of pains in the head and of coldness and numbness of the feet and hands. Had in earlier life been always healthy, and on admission was a healthy-looking vigorous man for his age. On July 9th, while engaged in berry picking in a field in Anne Arundel Co., Md., he suffered from heat stroke, remaining unconscious for two hours and having to be carried to his home. The next day he was up and about again, and felt able to work, but had not been altogether well since, having suffered from headaches and occasional chilly sensations.

On admission the following note was made: "Healthy looking, much sunburnt, pulse full, walls of blood vessels soft, no oedema of feet. The lungs are clear in front and behind; the expiration is a

little prolonged. The apex beat of the heart is neither visible nor palpable, the sounds are weak, the second being scarcely audible at the base. The area of liver dullness is reduced. The spleen is not enlarged; the urine is light yellow in color, specific gravity, 1010; no albumen, no casts."

Concerning the further progress of the case, we have the following account from Prof. Osler.

"I saw the patient only during the first four days of his stay at the Hospital, and thought that he was suffering from the effects of a sun-stroke. He was given a tonic mixture. The patient's temperature was normal, but on the 20th and 21st the morning records were 97.6° and 97.8° respectively.

On the 25th, at 11.30, he had a chill; the temperature rose to 105° and remained high all the afternoon. At 7.30 p. m. it was again 105°, and he was given a graduated bath.

Throughout the 26th the temperature fell, but did not go below 101°; the pulse was rapid and feeble.

On the 27th the temperature at 8 a. m. was 100.5°; in the afternoon it rose to 103°, and in the evening was 100.3°; pulse, 104, extremely irregular and intermittent. There were feeble râles, with a high pitched percussion note in the right infra-scapular region. Towards evening the patient sweated profusely and the breathing was of the Cheyne-Stokes type.

On the 28th the temperature fell rapidly, sinking from 103° at 4 p. m. of the 27th to 97.3° at 8 a. m. of the 28th, and to 95.5° at 10 a. m. The pulse was extremely feeble and irregular. He vomited twice. There has been no expectoration. The breath sounds at the right base have been very feeble. Throughout the afternoon of the 28th the temperature rose and at 8 p. m. was 100°.

On the 29th the Cheyne-Stokes breathing persisted, and the patient had slight diarrhoea. His speech was disturbed but he appeared to be conscious. Throughout the 30th, 31st and August 1st he sank gradually and died on the morning of the 2d.

I did not see the patient from the date of his chill until the morning of the 2d, just before his death. The case was regarded as one of low anomalous pneumonia. The day after the chill it is stated in the note that the blood was examined with negative results; but there is no initial to indicate by whom the examination was made."

Autopsy.—(Professor Welsh.) (Abstract from the records of the Pathological Laboratory).

Anatomical Diagnosis.—Malarial fever, with malarial parasites in the blood and spleen; soft, swollen, pigmented spleen; pigmented and myristicated liver; pulmonary emphysema; general muco-purulent bronchitis; pulmonary oedema; catarrhal colitis.

Exterior.—Body, 168 cm. long; much emaciated. Hernial tumor in each groin. Rigor mortis well marked. Livor mortis in dependent parts. On belly and chest are a number (20–30) dark red liver spots, slightly elevated, which do not disappear on pressure.

Abdominal Cavity.—Loops of small intestine lie loosely in the hernial sacs which open by wide mouths at internal inguinal rings into the peritoneal cavity. Spots of fibrous thickening on peritoneum covering mesentery of small intestine. Old pigmented patches on pelvic peritoneum. Firm old adhesions binding tightly together the under surface of the liver and gall-bladder with the adjacent parts of the duodenum and ascending and transverse colon. The capsule of the liver along its anterior border and on the adjacent convexity is opaque, white, thickened and wrinkled, owing to old fibrous thickening. The diaphragm on the right side reaches the lower margin of fifth rib, on left, lower margin of sixth rib. The peritoneal cavity contains about 50 cc. of clear yellowish serum.

Thoracic Cavity.—The anterior surface of the pericardium, save a triangular area much smaller than normal, is covered with the emphysematous lungs. There are old fibrous adhesions between the pleural surfaces of the posterior parts and apices of both lungs. On anterior surface of middle lobe of right lung are some old white fibrous nodules, the size of a pin's head and larger. There is a small amount of clear serum in each pleural cavity and also in the pericardial cavity.

Heart.—Weight, 290 grams; small; myocardium of a deep brown color; some thickening of aortic and mitral valves along lines of closure, but apparently not enough to interfere with the functions of the valves. Some atheromatous deposits in pockets of aortic valves. Endocardium of left ventricle thickened and opaque. No fibrous patches in myocardium except at tips of musculi papillares. Chordae tendineae of mitral valve somewhat thickened and retracted. The coronary arteries present near their origin moderate atheromatous

thickening, and are rather tortuous. Loose dark red clots and some decolorized post-mortem clots in both ventricles.

Lungs.—Markedly emphysematous, swollen, not collapsing readily, of a soft cushiony feel, air cells in anterior part of lungs near inner margin reach size nearly of pins' heads. Considerable pigmentation with coal. On section the dependent parts of lung are much congested and there is moderate general oedema. Both large and smaller bronchi contain much muco-pus, which can be squeezed out in opaque thick whitish drops. The bronchitis is general. The pulmonary parenchyma everywhere contains air. There is no pneumonia. On pleura at apices of both lungs are some old fibrous scars and immediately beneath the pleura are a few old black calcified nodules the size of split peas.

Spleen.—Weight, 192 grams; length, 13 cm.; width, 8 cm.; thickness, 3.5 cm. The capsule is extensively thickened and opaque, and the organ is surrounded by old fibrous adhesions. The consistence is soft, the organ being almost diffluent on section. Color, dark brown or blackish-brown. Malpighian bodies not readily distinguishable in the soft dark-colored pulp.

Kidneys.—Surface smooth, save some indication of foetal lobulation. Capsules not adherent. Cortex measures 6 mm. in thickness; striae distinct and regular. Weight of each kidney 196 grams. Dimensions, 10 x 5 cm. There is a small white fibroma the size of a split pea in cortex of left kidney. Adrenals apparently normal.

Bladder.—Contains about 5 cc. of whitish fluid. Mucosa normal. Prostate moderately enlarged and contains many corpora amylacea.

Liver.—Weight, 1650 grams. Dimensions, 24 x 15 x 6.5 cm. Capsule opaque and thickened along anterior margin. Prevailing color on section brown or bronzed. Centers of acini of a reddish brown, peripheries of a lighter brownish color. The gall bladder contains a moderate amount of brownish yellow bile; bile duct patent.

Pancreas.—Firm, pale, normal.

Large Intestine.—Rectum contains very hard, yellowish scybala coated with mucus. Balls of firm yellow faeces in colon and caecum. Mucous membrane of large intestine, particularly of sigmoid flexure and colon, coated with firmly adherent, stringy, very tenacious, white mucus, often peculiarly arranged in irregular anastomosing lines. The mucus is about of the consistence observed in the discharges of mucous or membranous diarrhoea.

Small Intestine.—Contains fluid or semi-fluid yellow material and presents areas of hyperaemia and of coating with mucus.

Stomach.—Contains a little partially digested food. Mucous membrane of pyloric region coated with a thin layer of mucus. On anterior wall, 4 cm. from pylorus, is a mucous polypus 6 mm. long, and 4 mm. thick, with a smooth, round extremity; not constricted at base. Near base of polypus is a round depression with smooth edges and floor communicating with an oblong depression by a narrow similar but elongated depression. The round depression is 3 mm. in diameter, the oblong measures 4 x 2 mm. These depressions extend in depth to about that of the mucous membrane. The floor of the depressions looks as if covered with smooth mucous membrane. There is no stellate cicatricial tissue in or near these depressions, nor is there any evidence of change on the outer surface of the stomach.

Brain.—Arteries of base very atheromatous; considerable increase of cerebro-spinal fluid; white substance of hemispheres presents numerous puncta vasculosa. Brain otherwise appears normal.

Microscopical examination of blood from finger shows a few pale bodies of shape and size of red corpuscles or larger, containing pigmented plasmodia; also free round pigmented corpuscles, the pigment in molecular movement (varying in size from blood plate to twice this size); also pigmented crescents, the pigment in a ring in the middle; in one specimen of splenic pulp two actively moving free flagella. In the capillaries of the brain are a few pigmented corpuscles.

Examination of the hardened tissues.—A microscopical study of the organisms and tissues confirms the findings at autopsy and the diagnosis of an aestivo-autumnal malarial infection. The unequal distribution of the parasites and especially the accumulation of immense numbers of them in the capillaries of the mucous membrane of the stomach render this case of more than ordinary interest.

The Liver.—On examination with very low powers (8 to 16 diameters) there are very few pigment masses large enough to attract notice; in marked contrast to what could be observed with these powers in the liver of Case C (tertian infection).

With higher powers intravascular phagocytes, especially macrophages, are seen to be comparatively few in number. The malarial parasites are not especially numerous in the liver. They vary in size, and have a yellow tint in tissues hardened in Müller's fluid; some

contain almost no pigment; others contain very fine granules of brownish black pigment; still others contain distinct dark central blocks of pigment. A few of the organisms appear to be free in the blood or included within red corpuscles. The majority are inside mononuclear leucocytes; a few have been taken up by polynuclear leucocytes. The latter cells also contain free pigment in granules and blocks. There is marked participation of the endothelial cells of the capillaries of the liver in the phagocytic process. These cells, the cells of Kupffer and the intracapillary macrophages contain a few parasites, pigment in granules and in blocks, infected and non-infected red corpuscles, fragments of corpuscles, and particles of irregular size and shape that yield the blue iron-reaction. Some of the phagocytic cells, especially the endothelial cells, contain *brassy* corpuscles (globuli rossi ottonati of the Italians). From many of the pigmented capsules in the larger cells fine lines of yellowish brown pigment can be seen radiating out into the protoplasm. The pigment is chiefly situated in cells at the periphery of the lobules. In certain areas bright yellowish pigment in considerable quantities can be seen running along the rows of liver cells. The liver cells themselves are large, swollen, finely granular and often vacuolated. The nuclei of the liver cells vary in size and in vesicularity. The central veins of the lobules and the neighboring capillaries are dilated and the liver cells near them contain brownish pigment. The spaces between the liver cells and the capillary walls are exaggerated. Some of the liver cells themselves contain malarial pigment. No areas of necrosis can be made out, but as no tissues from this case were preserved in absolute alcohol small necroses could easily be overlooked. There is a slight excess of lymphoid cells in the portal spaces, and a few larger pigmented cells are present in the connective tissue of these spaces.

The Spleen.—The blood vessels are distended, especially those of the pulp. In places there are actual haemorrhages into the pulp tissue, and numerous red corpuscles can be made out among the cells of the pulp-cords. The capsule of the spleen is slightly thickened and the stroma is denser than normal. There is an astonishingly large number of organisms present. These vary in size, and are of the aestivo-autumnal variety, the majority appearing to be nearly full grown. They are not numerous in the larger vessels of the spleen, but are very abundant in the blood of the smaller vessels of the splenic pulp.

A large number of well formed organisms, infected corpuscles, remains of organisms and corpuscles, and fine and coarse pigment are contained within phagocytes. The macrophages are of about the same size or a little larger than those described in the liver. Many of them contain *brassy* corpuscles. The endothelial cells and the cells of the splenic pulp itself, as well as the mononuclear leucocytes, contain foreign products. Here and there a large vesicular parasite with very little pigment is visible, and a few crescents can be made out, although they are probably much more numerous than the study of hardened tissues alone might have led us to infer. They were present in considerable numbers in the fresh blood taken from the spleen at autopsy, but on account of the deformity resulting from hardening and the pallor of the bodies of these forms, we have experienced the same difficulty in recognizing them in sections which has attended the studies of other observers. The pigment is mainly contained in the splenic pulp; the Malpighian bodies are comparatively free from it, and when pigment is to be made out in the latter, it is usually included within large cells around the arterioles.

The Kidney.—There is a moderate degree of chronic diffuse nephritis, some of Bowman's capsules showing slight fibrous thickening. The glomeruli for the most part fill the capsular spaces. A moderate amount of pigment is to be seen within the glomeruli, chiefly contained in the endothelium of the glomerular capillaries; some of it being within mononuclear cells inside the capillaries. The endothelial cells of the intertubular capillaries and of the small veins contain occasionally at the poles of their nuclei granules and masses of malarial pigment. Occasionally inside the vessels a mononuclear cell containing one or more tolerably well preserved organisms can be made out. No parasites were seen in the kidney outside of phagocytes. The epithelium lining the convoluted tubules is swollen and filled with fine granules. Some of the cells are actually necrotic, the nuclei refusing to stain. A number of the tubules in the cortex contain within the protoplasm of their lining epithelium masses of bright yellow pigment. Occasionally hyaline casts are met with in the collecting tubules.

The Stomach.—The findings in the sections of the stomach are of interest. The capillaries and veins of the mucous membrane are widely dilated, many of the larger and smaller veins being engorged with red blood corpuscles, whose outlines are perfectly well preserved,

and in certain areas inside nearly every red corpuscle is a parasite with a central block of brownish black pigment. Along with these masses of infected corpuscles there are often found numerous mononuclear macrophages crowded with blocks of malarial pigment like that to be seen in the infected corpuscles. There are places where the lumina of the veins appear to be narrowed near the base of the mucous membrane and as though blocked with macrophages damming back infected corpuscles. The arteries and veins of the submucosa are singularly free from infected corpuscles. The distribution of the parasites in the capillaries is very irregular; while in one area all of the capillaries may be closely crowded and distended with infected corpuscles, in other places quite near by the vessels may be almost entirely free from them. Besides the macrophages already described there are large red-corpuscle-carrying cells within the veins and capillaries, filled with blood corpuscles which stain intensely with eosin. These cells contain large single nuclei which often send out processes among the red corpuscles in the protoplasm. Some of the smaller vessels appear to have their lumina entirely filled with huge cells of the kind described, forming veritable casts. These cells must exercise considerable influence in obstructing the on-flow of blood. The surface of the mucous membrane in many places refuses to stain, and fragmented nuclei are visible evidences of superficial necrosis.

The Heart.—There is an excess of brown pigment at the poles of the nuclei of the muscle cells; otherwise there are no striking alterations.

Cerebrum.—Only an occasional infected corpuscle can be made out within the capillaries; a few of the endothelial cells lining the capillaries are phagocytic. Portions were saved from only one or two parts of the cortex.

Thyroid Gland.—In the vessels of this organ as elsewhere in the peripheral circulation it is rarely that infected red blood corpuscles are to be seen.

III.

CASE B.—*Aestivo-autumnal malaria; grave abdominal symptoms.*

John B., age 34, admitted to the Johns Hopkins Hospital, September 10th, died September 16th, 1890. The following is Prof. Osler's clinical note of the case:

"I saw him in the dispensary at 1.30 p. m. He was very weak and tremulous, with eyes congested, cheeks flushed, and with a dazed, stupid appearance. The tongue was swollen, heavily furred and indented. He looked like a man who had been drinking, and I told his brother that it would be impossible for us to admit him to the wards in his present state. He assured me, however, that he had not been drinking to excess, and on ascertaining that there was not the slightest trace of alcoholic odor in the breath, I signed the order for his admission.

The following history was obtained. Family and personal history good. The patient is a sailor by occupation, and has enjoyed excellent health; he left Boston for Savannah five weeks ago; spent a week in the latter place, and as the weather was oppressive he, with several of his shipmates, was in the habit of sleeping on the grass all night. He remained well on the voyage to Baltimore, where he landed August 31st. He was about the house all the week, though not feeling quite himself, but the present illness dates from Sunday the 7th, when, without any chill or fever, he began to have vomiting. He felt extremely weak and prostrated, so that he could not get up on Monday morning. Throughout Monday and Tuesday the vomiting continued at intervals and he was completely prostrated. He had no chills, but on Monday and Tuesday he took some quinine pills. In the dispensary, after failing to detect any alcoholic odor in his breath, and on learning that he had recently come from the South, the blood was at once examined; large numbers of Laveran's organisms were found, which rendered the diagnosis clear. His temperature on admission into the ward was 101°, pulse 104, small, tension not increased, radials not stiff. The abdomen was soft; nowhere tender. The edge of the spleen was just palpable on deep inspiration; upper border of dullness at the ninth rib.

Apex beat of heart in 5th interspace within nipple line; sounds clear; examination of the lungs negative.

Blood.—Small intra-corpuscular forms in extraordinary abundance, often 6 or 8 to be seen in the field of the $\frac{1}{12}$ im. The majority of them are not pigmented and undergo very rapid changes in outline. The pigmented forms have the granules more concentrated than is usual in this stage of the evolution of the parasites. An unusual number of the leucocytes present pigment granules.

11th. Very bad night; much vomiting; temperature sank to 98.6° at 10 p. m., and to 98.2° by 8 a. m. At the morning visit the patient looked depressed; tongue heavily furred; pulse 80, small and thready; respirations 20. Had no headache and complained chiefly of profound weakness. At noon the temperature began to rise and at 4 p. m. reached 102.2°, and for 6 or 8 hours remained about 102°, gradually falling through the early morning hours and at 8 a. m. reaching 98.5°. The blood condition remains practically about the same.

12th. 10 a. m. Patient passed a better night. The vomiting has stopped but the tongue is still furred; no increase in the splenic dullness. The bowels have been freely opened. He still looks depressed and dull, and complains of a feeling of great prostration.

13th. Temperature has been about 98° for the past 24 hours, pulse 72, small. The vomiting has not been so distressing, and he has taken the milk and brandy better than on any day since admission. The blood examination shows a marked diminution in the number of corpuscles containing the plasmodia, the diminution being doubtless due to the influence of the quinine.

14th. Temperature has been subnormal, not rising above 97.5° all day. The vomiting has returned, and for the first time the vomitus contained blood, not in large amount, but sufficient to color the fluid. His mind is perfectly clear, and his sole complaint is of the extreme depression.

15th. 10 a. m. Patient's condition is worse since 8 p. m. last evening. The temperature has been below 97°, and at 12 midnight sank to 96°; pulse, 64; respirations, 20. Tongue still swollen, heavily furred and indented. Note on the blood to-day is: "plasmodia very much diminished in number. Leucocytes still show much pigmentation." The urine is amber colored, specific gravity, 1010; acid, contains a slight amount of albumen. At 9 p. m. I made the following note: "Patient is in a very peculiar condition; is drowsy, dull, roused with difficulty, and does not answer clearly. He has behaved oddly all day, and has been very restless. There has been very little vomiting; temperature has been subnormal, and is now 96.5°. For the first time the tongue is distinctly dry."

16th. Through the night the patient was very restless and had much hiccough; was not delirious, but acted queerly. The tempera-

ture sank through the night, and at 2 a. m. was 96°; at 4 a. m. the thermometer could not be made to register more than 95°, and the temperature remained at this point until 10 a. m. The vomited matter last night contained flakes of blood enough to tinge the whole fluid. He had retention of urine and this morning 1500 cc. were withdrawn, which showed a narrow ring of albumen and contained hyaline and granular tube-casts. The nurse says that he does not understand questions, but he seemed to recognize me, and gave fairly rational answers, but complained of great oppression in the abdomen. The pulse is 72, and considering his condition the volume and tension were remarkably good. At 6 p. m. I made the following note: "Temperature has risen through the day and is now 97.2°. The tongue is dry, pulse 96, regular and of very fair volume. He is extremely restless, and his face has a dusky hue; the respirations are at times gasping, 24 to the minute. He answers questions, but talks and rambles in an incoherent way. To-day very few red blood corpuscles have been found containing plasmodia; the leucocytes are still much pigmented." Patient became much more restless, threw himself about on the bed, then became unconscious, and died at 8 o'clock. The treatment consisted of half-drachm doses of quinine every six hours, which was given hypodermically when the vomiting became excessive.

Autopsy 15 *hours after death.*—Body 161 cm. long, well nourished, post-mortem discoloration of dependent parts and of face and neck. Peritoneum smooth, a little darkened and slaty in appearance, no excess of fluid in abdominal cavity. No pleural adhesions; pericardial and pleural cavities dry. Right side of heart distended with fluid blood; left ventricle empty and contracted. Heart valves all normal except for slight atheroma at attached borders of aortic cusps. Myocardium pale, otherwise normal; left lung crepitant, anteriorly and in lower part of upper lobe congested and oedematous. Right lung still more oedematous, deeply engorged at base. A small piece cut from extreme posterior part of lower lobe on this side sinks in water. The bronchi contain frothy mucus.

The Spleen and Liver.—The spleen measures 8 x 13 cm., is extremely soft, almost diffluent. The pulp is of a dirty brownish-red hue; the capsule is thin and shows a few superficial hemorrhages. The liver is large, slate-gray in color; its capsule is slightly thick-

ened and opaque. Just above the gall bladder on section the substance is moderately firm and has a uniform bronze or slaty tinge. The outlines of the lobules are not well defined. There is deep pigmentation about the portal canals and the smaller bile ducts are distended.

The Kidneys are large and swollen; the surfaces are mottled. The capsules are adherent in places. On section the consistence is firm. The Malpighian tufts are prominent and congested; the medullary rays are pale and between them the lines of vessels are deeply reddened. No areas of opacity are visible. The cortex is distinctly though slightly pallid. The adrenals show no marked alteration.

The Stomach.—Contents are liquid and of a yellowish color. The mucous membrane has a slatish-grey tint, and on the anterior surface near the lesser curvature are the scars of two small ulcers and on the posterior wall three other flat cicatrices are visible. The bile duct is patent and the portal vein is free. The contents of the small intestine are reddish-brown in color, the mucous membrane is congested in places. Peyer's patches are not swollen, although the lower ones have a shaven beard appearance. The colon is deeply congested in places and covered with tenacious yellow faeces. There is no intestinal ulceration.

The Brain.—The dura presents on its surface well back on the right side a small hemorrhage. The pia over the cortex is smooth, in it, over the middle of the first right frontal convolution close to the longitudinal sinus, is an area of brownish-black pigmentation about 1 cm. in diameter. The membranes and vessels at the base appear normal. On section the substance of the brain looks natural except for turgidity of the vessels.

Microscopical Examination.—The Liver.—The malarial pigment is situated chiefly in the outer half of the lobules and is principally enclosed in cells. The liver capillaries are engorged with blood. In some of these many of the red corpuscles contain malarial parasites which vary in size from extremely minute forms to larger bleb-like organisms almost as large as the corpuscles. Some of these parasites contain only a little fine pigment; others none at all. Some of the liver capillaries are quite free from parasites, while others are crowded with organisms each containing a central block of brownish-black

pigment. A few of the intra-corpuscular organisms not enclosed in phagocytes show fine lines of yellowish pigment granules radiating from them, which appear sometimes to extend beyond the limits of the corpuscle in which they are contained. Most of the organisms are contained within cells. In this case the endothelium of the hepatic capillaries and the cells of Kupffer have played the greatest rôle in the phagocytosis. There are some large mononuclear intra-vascular phagocytes, but most of the organisms and the remnants of organisms are contained within the protoplasm of the endothelial cells, being often, though not always, situated at the poles of the nuclei. In the intra-capillary macrophages, which are of smaller size than those occurring in the liver of Case D, the nucleus is frequently surrounded by black pigment blocks. The swelling of the endothelial cells of the capillaries is marked, being sufficient, one would think, to offer serious impediment to the progress of the blood. The liver cells themselves are swollen and granular, and many of them are filled with yellow pigment masses. In places they are atrophied and the capillaries in the atrophied areas are correspondingly dilated.

The Kidneys.—All the blood vessels of these organs are dilated, the veins of the pyramids being especially wide. There is irregular dilatation of the glomerular capillaries. Comparatively few parasites are present in the kidneys, although some distinct forms are visible within the veins and capillaries. A small number of phagocytic cells can be seen (intra-vascular phagocytes and endothelial cells). The capsules of some of the glomeruli have undergone fibrous thickening; in places the capsular endothelium is proliferated. The epithelium of the convoluted tubules is swollen and granular, and there are numerous hyaline casts to be seen in the small collecting tubules. In the pyramids haemoglobin casts can be made out.

The Brain.—A few infected corpuscles can be seen within the blood vessels. Here and there a phagocytic endothelial cell occurs. In one spot there is a very small infarct showing necrosis of the cerebral tissue, hyperaemia at its margin, and an accumulation of mono- and polynuclear cells. There are no other marked changes.

No other tissues were saved from this case. This is unfortunate, since from the grave gastric symptoms observed during life an examination of the contents of the capillaries of the mucous membrane of the stomach would have been interesting (vide Case A).

IV.

CASE C.—*Acute aestivo-autumnal malaria; death from accident; acute necrotic lesions in the liver and spleen. Remarks on the relation of malaria to cirrhotic processes.*

R. G., aet. 22. Pole, single, laborer, admitted to Prof. Osler's wards October 5th, 1892. He complained of chills and fever, and on entrance was suffering from a paroxysm, during which his temperature reached 106.8° F. He had been working at Locust Point (a part of the city near the harbor in which malarial infections frequently occur) when he was taken ill, two weeks before his application to the Dispensary for treatment. On admission his blood was examined and found to contain only a few hyaline intra-cellular parasites.

The physical examination of the heart and lungs yielded no abnormal signs. The respirations were hurried, the pulse was frequent and slightly dicrotic. The lower edge of the spleen could be easily palpated, reaching a point two fingers-breadth below the costal margin. The liver dulness was not increased. The patient vomited everything taken into the stomach, including the quinine administered, so that other methods of exhibiting it had to be resorted to. On the next day the blood was carefully examined twice, but no malarial parasites could be found. The leucocytes were not increased in number. The patient complained of severe abdominal pain on the following day; two slides of blood were examined in the early morning but no malarial parasites could be found. The patient met with an accident, associated with profuse hemorrhage, and died in the afternoon.

At the autopsy, which was made by Dr. Flexner while the body was still warm, the typical lesions of an acute malarial infection were found. There were numerous ecchymoses scattered over various parts of the skin and over the serous membranes. The muscles were brownish-red in color. The lungs were moderately pigmented; the heart valves were normal. Heart's flesh pale. Anterior mediastinal glands softened and reddened.

Liver.—Weight, 2200 grams; surface smooth; substance of a dark brown color; consistency soft; lobules invisible.

Spleen.—Weighed 800 grams; measured 23 x 11 x 5 cm.; diffluent; deep dark red in color; Malpighian bodies visible; pulp abundant.

Pancreas and *kidneys* normal; *stomach, intestines* and *bladder* normal. Lymph glands in hilum of spleen and about the pancreas swollen, softened and deeply congested. Culture tubes of agar-agar inoculated from various organs at the autopsy remained sterile.

The Spleen: Microscopic Examination.—The lesions in this organ resemble much those seen in certain acute bacterial infections. The organ, especially the pulp, is markedly hyperaemic. In places there are evidences of extravasation. On examining the pulp with higher powers the contents of the capillaries and veins are seen to be complex. Besides large numbers of ordinary red blood corpuscles there are a number containing malarial parasites of the aestivo-autumnal type. The majority of the latter, however, are enclosed within mononuclear cells. Well preserved organisms are by no means numerous and the contents of the phagocytes consist largely of remains of malarial organisms and shrunken corpuscles containing more or less brownish-black pigment. The number of red blood-corpuscle-carrying cells is much increased; huge cyst-like cells, usually mononuclear, the nucleus sometimes having radiating processes which run out toward the periphery of the cells, are seen sometimes containing thirty, forty, fifty or more apparently well preserved red blood corpuscles which stain deeply in eosin. The pulp cells themselves are large and swollen, and frequently contain within their substance other cells, chiefly with nuclei of the lymphoid type; sometimes also polynuclear leucocytes, and very often a number, five, ten or even more completely colorless red blood corpuscles. These cells contain in addition infected red blood corpuscles, free malarial parasites, the more or less broken down remains of parasites and free malarial pigment often arranged in dotted lines. Besides these large mononuclear cells in the vessels there are very many small and large lymphocytes seen crowding the lumina of the vessels. There are also a few polynuclear leucocytes, some ordinary large mononuclear leucocytes, and an occasional giant cell with budding nuclei, resembling those normally present in the bone marrow. The protoplasm of many of the cells in the pulp-cords stains deeply in eosin. Sometimes the protoplasm of these cells is highly refractive and the nucleus does not stain at all, or it may be broken up into a number of fragments irregular in size and shape. In these cells one or more polynuclear leucocytes are often to be seen, the hyaline protoplasm being sometimes closely crowded with them.

In some places in the pulp there are actual focal necroses, very much like those which are to be seen in typhoid fever. In these, particularly in the more recent ones, large necrotic cells with hyaline protoplasm and fragmented nuclei can be made out along with lymphoid cells, polynuclear leucocytes and endothelioid cells. In the larger necroses the necrotic cells may be almost entirely obscured by the collection of lymphoid cells and the leucocytes with polymorphous nuclei. In these areas there is evidence of division by amitosis with distortion of the nuclei (abschnürungsvorgänge), and scattered among the cells a number of minute nuclear fragments are visible. There are also in these areas large phagocytes containing within their protoplasm malarial parasites and pigment, polynuclear leucocytes, intact and broken down red blood corpuscles and nuclear fragments.

The endothelial cells lining the vascular spaces are evidently phagocytic. They contain within their protoplasm, usually at the poles of the nuclei, the remains of malarial organisms, broken down blood cells, free malarial pigment, and irregular masses of blood pigment which yields the blue iron reaction. The Malpighian corpuscles themselves are swollen; there has been proliferation in the lymphoid cells. Among the lymphoid cells can be seen a few large cells resembling somewhat the cells of the pulp, often containing within them mononuclear and polynuclear cells, red blood corpuscles, and sometimes malarial organisms and malarial pigment. These are best studied in specimens stained with methylene blue and eosin. Numerous capillary thrombi can be made out scattered through the spleen; these thrombi resemble closely those seen in the liver of this case. One is tempted to think of a relation existing between these capillary thrombi and the focal areas of necrosis.

The Liver.—The capillaries generally are dilated, in some areas more markedly than in others. Within the capillaries are many red blood corpuscles, a few red blood-corpuscle-carrying cells, lymphoid cells, small and large, a few polynuclear leucocytes, and in some parts of the liver large phagocytes. The latter may contain within their protoplasm, besides well formed malarial parasites of the aestivo-autumnal type, shrunken remains of parasites, fine malarial pigment, red corpuscles, particles of haemosiderin, lymphoid cells, and occasionally polynuclear leucocytes. The endothelial cells lining the

capillaries are in places much swollen, their nuclei are large and vesicular, and within their protoplasm are sometimes visible the same substances as those mentioned as occurring within the intra-vascular phagocytes. The endothelial cells are so much swollen in places that they materially narrow the lumina of the capillaries. The spaces between the capillary walls and the liver cells are wider than normal and there is a considerable degree of atrophy of the rows of liver cells. The liver cells contain an excess of brownish-yellowish pigment. Some of the liver cells have giant nuclei. The cells of Kupffer, between the capillary walls and the rows of liver cells, are swollen and some of them are evidently phagocytic. Occasionally lymphoid cells are visible in the spaces between the capillary walls and the liver cells. The findings within the lumina of the hepatic capillaries are of interest. The number of cells with nuclei of the lymphoid type is astonishing. Many of these are of the size of ordinary lymphocytes, others being somewhat larger. Occasionally cells containing basophilic granules within their protoplasm are visible within the capillaries, and in one or two instances they are seen included within the protoplasm of makrophages. In one section two or three cells within the capillaries possessed budding nuclei quite like those of the giant cells in normal bone marrow. One of these of large size appeared to be acting as a phagocyte as it contained within its protoplasm malarial pigment and a single mononuclear cell. Some of the phagocytes which are partially or completely necrotic are surrounded or invaded by leucocytes with polymorphous nuclei. A number of the endothelial cells are also degenerated or necrosed. Single and multiple liver-cell-necroses occur scattered throughout the section, forming necrotic areas of varying sizes, sometimes as large as those seen in typhoid fever. When one or two liver cells only are necrotic the lesions are tolerably distinct. The nuclei of the necrotic cells are fragmented or absent and those of the neighboring liver cells may be shrunken and deeply stained. The protoplasm of the cell is hyaline, stains deeply in eosin, and may be invaded by polynuclear leucocytes.

In larger areas the pictures are more complex and somewhat difficult to explain. The necrotic liver cells have either been removed or are obscured by the accumulation of other cells. In these foci usually, however, the remains of liver cells and of their nuclei are visible, especially in the periphery. Accumulated here are a number

of cells with small sharply stained nuclei, lymphoid cells, polynuclear leucocytes, and spindle-shaped cells with vesicular nuclei. In addition there may be large phagocytic cells containing lymphoid cells, polynuclear leucocytes, red blood corpuscles, nuclear fragments, and sometimes malarial pigment. It is no easy matter to decide as to the origin of all these different cells, although with thin sections and careful study the source of most of them can be made out. It is not always possible, however, to say what are endothelial cells and their derivatives, and what are to be regarded as blood cells and their derivatives. Some of the small deeply stained nuclei are probably to be looked upon as the offspring of leucocytes which have divided *in situ* by amitosis, as the nuclei of these cells show various distortion processes (abschnürungsvorgänge). Sometimes a cell with hyaline protoplasm and a degenerating nucleus can be seen surrounded by a number of cells whose protoplasm overlaps and seems actually to be mingling with the protoplasm of the degenerating cell, although on close focusing the boundaries of the various cells can usually be made out. The cells inside necrotic cells frequently show fragmented nuclei and hyaline protoplasm. The number of cells inside a single dead liver cell varies. In one the nuclei of ten foreign cells, most of them polynuclear leucocytes, were included, and the nucleus of one of these latter was fragmented.

There are numerous thrombosed capillaries to be made out in thin sections (vide Plate V, Fig. 1). Sometimes a single capillary appears to be occluded, and a few leucocytes with distorted nuclei are seen lying in the thrombus. In other places two or more neighboring capillaries are plugged, and in addition to the white cells in the thrombus, leucocytes, mono- and polynuclear, can be seen aggregated in considerable numbers in the neighboring capillaries. There may be a diminution in size, evidences of degeneration, or a total disappearance of neighboring liver cells. Plate V, Fig. 2 shows the condition better than any description. The occurrence of so many of these thrombosed capillaries in the same sections with the areas of focal necrosis is suggestive, and one is very much tempted to look upon the larger areas of necrosis as advanced stages of a process which began with capillary thrombosis.

The triangular portal spaces present a very peculiar appearance. The connective tissue is crowded with cells containing nuclei of the lymphoid type so that the tissue reminds one of the structure of ordi-

nary lymphoid tissue. In the adventitia of the portal vein contained apparently in loose spaces are very many lymphoid cells. The portal veins show in section many mononuclear and a few polynuclear leucocytes, besides many makrophages such as have been described in the splenic veins and in the liver capillaries. There were no lesions of tuberculosis anywhere in the body, and no bacteria were demonstrable by cultural methods or in sections of the organs.

The Kidney.—The lumina of the convoluted tubules in the labyrinth are wide, and the projecting epithelium lining them is somewhat swollen. The glomeruli do not completely fill the capsular spaces; in some of the latter coagulated albumen may be seen. Some of the tubules in the medullary rays contain in their lining epithelium yellowish pigment. The kidney is almost free from malarial organisms and from malarial pigment, although occasionally a brownish-black particle is visible in a glomerulus.

The Mesenteric Lymph Glands.—The lymph sinuses, especially in the medulla, are wide and are filled with cells. These cells for the most part irregular in shape contain vesicular nuclei and an abundant protoplasm which stains in eosin and they resemble in general the endothelial cells which normally lie upon and are wrapped around the reticular framework. There are also many large and small lymphocytes and a few red blood-corpuscle-carrying cells. Some cells like those filling up the lymph sinuses can be seen among the lymphoid cells in the lymph follicles and cords. They occasionally contain within their protoplasm malarial organisms and their remains.

This case, it would seem, may be of help in explaining the relation of malaria to cirrhosis of the liver and allied diseases.

Even in the early descriptions of malaria the important influence of the disease as a causative factor in the production of chronic interstitial inflammations of some of the internal organs, and especially of the liver and kidneys is mentioned. Frerichs and Lanceraux both believed in a chronic hepatitis of paludal origin. Kelsch and Kiener working at the disease without any appreciation of the importance of the malarial parasites laid stress upon the changes in the liver secondary to malaria and describe both parenchymatous and interstitial forms of hepatitis. They refer to three varieties of the latter and discuss at length the character and distribution of the lesions in the liver. These same authors describe two main types of chronic disease of the kidneys

dependent upon malaria, the first, a diffuse malarial nephritis or glomerulo-nephritis, and the second, a nephritis characterized by a small granular kidney. Bartels, Rosenstein, Bouillaud, and others had early referred to the relation existing between malaria and chronic disease of the kidney. Laveran emphasised a chronic interstitial pneumonia of malarial origin, and Durozier in 1870, and also Kelsch and Kiener referred to the frequent occurrence of vegetative or ulcerative endocarditis in chronic malaria and believed that the lesions of the heart valves might be directly referable to the action of the malarial poison. Finally, chronic degenerative and fibroid processes in the spinal cord and brain have been attributed by some authors to malaria.

On the other hand, by not a few authors the possibility of cirrhotic processes being due to malaria has been stoutly denied. It has been justly claimed that in many of the cases reported as instances of chronic inflammation due to malaria insufficient attention has been paid to the possible responsibility of other etiological factors, such as alcoholism, syphilis, and tuberculosis.

Dr. Osler has particularly pointed out the difficulty of saying in a given case of cirrhosis of the liver or kidneys that malaria has been the cause, and in his experience the association of malaria with cirrhosis has been very uncommon. Dr. Welch has seen only one case of malarial cirrhosis of the liver in New York, and that was in an Algerian.

The foregoing study has, however, convinced me that there are conditions present in malaria which are generally recognized as being capable of giving rise to chronic fibroid processes, and it would be strange did the latter not occur more or less frequently. Bignami in a very careful study of chronic malarial cases in Italy has come to a similar conclusion and traces with much acumen the chain of events from the onset of an acute malarial infection to the development of a cirrhotic process.

A careful consideration of the various phenomena associated with acute malaria will show that there are many ways in which a chronic interstitial inflammation could arise. Thus looking upon the chronic interstitial inflammations as being due most often to a primary degeneration of certain of the tissue elements, the new growth of fibrous tissues being secondary, we can think of many possible causes of the

former. Thus, the profound changes in the character of the blood serum consequent upon the alteration and destruction of large numbers of red blood corpuscles and leucocytes, the intermittent hyperemia in the viscera, the setting free of the malarial pigment, and the accumulation of the latter in the cells and tissues, the multiple capillary thromboses which sometimes occur, the disturbances of digestion in many of the cases, the areas of necrotic cells which can be demonstrated in liver spleen and kidneys, these are sufficient to convince one of the existence of many possible injurious influences.

The evidences in favor of the idea that the parasites produce definite toxines and that large quantities of these are set free during segmentation after each paroxysm is already considerable. The clinical phenomena in general and especially the increased toxicity of the urine after the paroxysm would seem to point to this. It must be remembered, however, that as yet no toxine has been proven to be formed by the parasite. It matters little, however, whether the toxic substances are produced by the parasites directly, or are in part the indirect result of their action upon the red blood corpuscles, the white cells or tissue juices. There is sufficient evidence that some toxic agent is at work. The cloudy swelling seen in the organs, the fever, the acute splenic tumor, but more especially the actual necroses early demonstrable under the microscope, make it impossible to doubt this fact.

In our description of Case C we have referred to the extensive focal necroses in the liver and in the spleen. Single cells, small groups of cells and quite large areas of cells were found in a state of hyaline necrosis where the nuclei refused to stain and the protoplasm showed an increased affinity for acid dyes. In such necrotic areas numerous cells were present, some of them leucocytes with polymorphous nuclei, others small mononuclear cells. In some of the older ones spindle-shaped cells could be seen. Fragmentation of nuclei and phagocytosis were visible, and there were multiple capillary thrombi to be made out. We have referred to the extensive necroses of the spleen pulp cells, of the red blood corpuscles and of the leucocytes. In many bacterial infections similar areas of necrosis have been proven to be due to the toxines which the bacteria produce. Reed for typhoid fever and Welch and Flexner for diphtheria have shown that the soluble products of the bacilli alone circulating in the blood are

capable of giving rise not only to diffuse parenchymatous changes, but also to definite focal lesions, areas of cell-death of varying size. Later Flexner, experimenting with blood serum, has shown that the serum of one animal will produce focal necroses in the liver kidney and spleen of an animal of a different species when injected intravenously into the latter. He further proved that these focal necroses could later result in the production of chronic interstitial processes in the liver and kidney.

In the liver, following the necroses, there was such an accurate reproduction of the cirrhosis seen in human beings that, as he put it, "a separate description seems superfluous." Areas of newly formed and forming connective tissue proceeded from the portal spaces, and also from the capsule; these were irregularly distributed throughout the organ. Newly formed bile ducts were numerous; but what was of particular moment was the association with these of another process, namely, acute degenerative changes in the liver substance which were distinctly to be recognized as the starting places of the cirrhotic processes. "The necroses and disintegration of the liver cells with emigration of the leucocytes went directly over into the new growth of fibrous tissue. New fibrous tissue could be formed within lobules, apparently independently of the inter-lobular connective tissue and of the capsule, just as there are independent foci of necroses in this situation."

It is easy to understand how the normal serum of the individual could be altered by the disease so as to become definitely toxic. Aside from the increased toxicity of the serum due to the presence of malarial toxines, the destruction of large numbers of red blood corpuscles and the setting free of young parasites, of pigment, and of masses of haemoglobin, cannot fail to be of considerable import. And although there is no experimental evidence bearing on this point, it is not impossible that the *isotonie* of the blood serum could be so affected as to lead to serious alterations not only in the constituents of the blood but also in the cells of the organs. That haemoglobinaemia and haemoglobinuria occur sometimes in malaria is well known. Haemoglobinaemia alone can give rise to an acute splenic tumor, or to an acute nephritis, as is well known in cases of poisoning by the chlorate of potassium and in the intoxication of one animal by the blood serum of an animal of a different species. The alterations in the functions of the spleen, liver,

and alimentary canal could easily lead also to important changes in the blood serum.

The relations of the melanaemia to cirrhotic processes is worth considering. The malarial pigment tends to accumulate in the periphery of the hepatic lobules and in the trabeculae of the spleen. It remains, too, for some time after the infection has disappeared, and it is not impossible that the irritation caused by the presence of this pigment could give rise to a chronic interstitial inflammation, perhaps analogous to the pneumonoconioses. It seems less probable, however, that the pigment is responsible for a new growth of fibrous tissue than that the latter is secondary to degeneration due to toxic effects.

It has been generally believed that any pathological condition which leads to an intermittent hyperemia of an organ may give rise to a chronic interstitial inflammation. In malaria there can be but little doubt that there is variable hyperemia of the liver and spleen with the paroxysms, just as the size of the spleen and liver varies in recurrent attacks of malaria.

The capillaries in the liver spleen and kidney are frequently found dilated especially in certain areas. Whether this is at all dependent on the distribution of the makrophages it is difficult to say.

Finally the influence of the disturbances of the digestive processes in malaria must not be omitted in considering the etiology of cirrhotic inflammations. There is general obstruction in the tributaries of the portal vein, and this alone would suffice to materially alter the assimilation. But in addition, as we have seen, the vessels of the mucous membrane of the stomach and intestines may be occluded in certain cases by thrombi of parasites or of infected red corpuscles. In some instances the nutrition may be so interfered with that the mucous membrane becomes necrotic. Undoubtedly in such instances substances absorbed from the lumen of the alimentary canal are far from normal.

There can be no doubt, considering the comparative rarity of cirrhosis following malaria, that the individual pre-disposition must be an important factor in those cases in which it occurs. Associated alcoholism or arterio-sclerosis for example might render the tissue cells less resistant to the poisonous substances, whatever they may be, or prevent the normal processes of repair.

That there may be different kinds of cirrhosis of the liver following malaria is not impossible. Thus there was no obvious relation in

Case C between the enormous increase in round cells in the portal spaces and the focal necroses or the capillary thrombosis. Nor was there any evidence that the round cells were being converted into fibrous tissue. Still these collections were quite like those which one sees in fresh nodules of cirrhosis of the liver. Dock has observed a similar extensive perivascular portal infiltration in a very acute case of malaria in a young man.

V.

CASE D.—*Double tertian malarial infection, associated with general streptococcus infection; symptoms of an acute nephritis with general anasarca manifested during life. Remarks on the bacterial infections and protozoan invasions which may be concurrent with malaria.*

Abstract of clinical record. (Prof. Osler.)

L. W., aet. 23, oysterman, married, admitted January 9th, 1892, complaining of shortness of breath with general dropsy. Family history unimportant. Patient has been previously healthy; denies syphilis; gonorrhoea nine years ago. Has never used alcohol in excess. Some three months before entrance, his work required him to stand in cold water daily for about two weeks. At the end of this time he noticed that his feet and body began to swell, that his urine was scanty and high-colored, sometimes even bloody, and that frequently he had to rise two or three times during the night to urinate. Somewhat later he observed that he was becoming short of breath, especially on exertion. Three weeks before admission he had a severe shaking chill, the first during his illness, and for the next two weeks he had chills nearly every day. During the past week, he states that he has had no chills. The dropsy has gradually increased, and the dyspnoea has become progressively more intense. Of late the urine has not been bloody, and the amount, he thinks, is larger than formerly.

Temperature on admission, 97.8°. Pulse under 100. Anasarca general. Patient rather dull and stupid. Pilocarpine $\frac{1}{6}$ gr. hypodermically repeated once caused profuse sweating.

Note dictated October 1, 1892.—"Medium sized man of good musculature; lips and mucous membranes a little pale; tongue coated; face

much swollen; feet and legs oedematous. Abdomen a good deal distended. Respirations, 24; pulse, 84.

Thorax.—Percussion, resonance good in front; deficient behind at right base where vocal fremitus is absent and the respiration is distant. On auscultation the sounds are clear in front; behind and in the axillæ numerous fine râles are audible. Heart sounds clear at apex and base.

Liver dulness merges almost directly into colon tympany at the 7th rib. Splenic dulness begins at the 8th rib. Though uniformly distended the abdomen is tympanitic and no movable dulness can be obtained.

Urine.—Dark in color, 1000 cc. in amount. Sp. gr., 1017; albumen abundant; many hyaline, darkly granular and epithelial casts present."

This case was looked upon clinically as one of acute nephritis. The existence and character of the fever were noted as unusual.

Dr. Osler, in commenting on the case in clinic, alluded to the existence of the fever, the mode of onset, and to the occurrence of chills, and stated that the existence of malaria was negatived by the absence of plasmodia from the blood. Unfortunately, through a misunderstanding among the assistants, each believing that the other had looked for the parasites, no examination of the blood had been made.

By January 23rd, the patient had become more oedematous. The pulse was 140; fluid was now demonstrable in the right pleural sac and in the peritoneal cavity. The urine still contained large quantities of albumen and casts. The fever persisted and was rather remittent in type ranging between 99° and 104° F. Hot baths, diluents and diuretics were given.

On the 24th and 25th the patient was much worse, took nourishment badly; the respirations were rapid and the pulse was feeble. The general anasarca became extreme and there was marked conjunctival oedema. The heart sounds remained clear throughout the whole course of the disease. Death occurred on the 26th of January, seventeen days after admission.

Autopsy. (Dr. Councilman.)

Anatomical Diagnosis.—Acute malarial fever; general streptococcus infection; subacute Bright's disease; malarial pigmentation of organs; chronic passive congestion; general anasarca; infarctions of kidneys; erysipelas.

Body of strongly built light mulatto; face and neck markedly oedematous; livor mortis in dependent parts; general subcutaneous oedema; scrotum markedly swollen. On the left shoulder, and on the inner aspect of both thighs there are blebs containing clear straw-colored liquid surrounded by areas of reddish discoloration.

The peritoneal cavity contains about one litre of straw-colored fluid, which contains large soft clots. The pleural cavities also contain a considerable amount of serous fluid.

Heart of medium size, chambers contain fluid blood and soft clots; weight, 300 grams; myocardium dark reddish-brown in color; all valves normal. Aorta abnormally small and thin, measuring in circumference, just above valves, 4.5 cm.; at middle of thoracic aorta, 4 cm.; at diaphragm, 4 cm.; at bifurcation, 2.75 cm. The common iliac vessels measure 2 cm. in circumference; the left subclavian, 1.9 cm.; the innominate, 2.5 cm. Pulmonary artery normal.

The Lungs.—The surfaces of both are smooth, and both are crepitant throughout. The consistence is increased, color dark red, moderate coal-pigmentation.

The Liver.—Weight, 1600 grams; dimensions, 25 x 16 x 8 cm.; Surface smooth; exquisite outlining of lymphatic network on surface. Consistence about normal. Color on section dark chocolate-brown color. Lobules visible.

The Spleen is small, weighs only 100 grams; size, 12 x 7 x 3 cm.; capsule smooth, not much thickened; consistence very firm. On section the substance is almost black, of a much darker tint than the liver. The Malpighian bodies are not visible. The trabeculae are visible and apparently increased in thickness.

The Kidneys together weigh 400 grams. They are both alike in size and general appearance. On the surface of each a few small fresh infarctions with hemorrhagic margins are visible. The capsules strip off easily. The general color of the external surfaces of the kidneys beneath the capsules is yellowish-brown, marked by scattered opaque darker areas, and here and there by minute hemorrhages. The whole kidney has a rather soft oedematous feel. On section the cortex has a yellowish appearance and is rather translucent; pyramids reddened, contrasting sharply with the lighter colored cortex. On some parts of the cortex the striae are well marked, in others they are less apparent or invisible. Average width of cortex 1 cm. A small amount of

fluid exudes from the cortical substance on pressure. The glomeruli are indistinct. The pancreas is oedematous. The adrenal glands are normal in size but it is noticeable that they are darker in color than normal.

The stomach is moderately dilated; both it and the intestines contain an excess of mucus. The intestines are generally distended and their walls are oedematous.

The bone-marrow is intensely pigmented, reddish-brown in color. The brain is small, especially in the frontal regions; weight, 940 grams. The pia is firmly adherent. No marked pigmentation. No hemorrhages or focal disease.

The Blood.—Examined fresh from the peripheral veins and various internal organs showed enormous numbers of malarial parasites, most of them nearly full grown, others only half grown (tertian type), many of them enclosed within the protoplasm of large mononuclear leucocytes. No flagella seen.

Frozen Sections of the kidney show a very little fat in fine droplets in the glomeruli. The epithelial cells of the tubules in the labyrinth are much swollen and are filled with fine albuminous granules and hyaline droplets.

Many of the tubules are dilated and are lined by low epithelium. Casts are numerous in sections and in urine collected from the bladder. Coagulated albumen is visible in the capsular spaces, in frozen sections made from bits of kidney previously fixed in boiling water. The capsular epithelium is swollen and evidently proliferated.

Bacteriological Examination. (Dr. Flexner.)

Cover slips from the heart's blood prepared and stained in the ordinary way showed numerous chains of streptococci.

Cultures.—At the autopsy, the surface of the organs was burned with a hot knife, punctured through the burned area, and tubes of agar-agar were inoculated from the internal tissues. Esmarch roll-tubes were employed; after being kept in the thermostat for twenty-four hours at 37° C they were examined with the following results: The tube from the lung was found to be closely crowded with extremely minute colonies of streptococci, no other micro-organisms being present. The heart's blood, kidney, liver, bone-marrow and spleen all yielded many colonies of streptococci, here also in pure cultures. The tube from the spleen contained many more colonies than that from the liver.

The tube inoculated from the bile contained a few—about one dozen—colonies of streptococci. Tubes were also inoculated from the fluid in the erysipelatous blebs and from the oedematous subcutaneous tissue at their margins. In those from the latter a pure culture of streptococci was obtained.

Microscopical Examination.—The Liver.—In sections examined with very low powers (8 to 16 diameters), it is easy to make out dilatations of the central and sublobular veins and of the capillaries about the central veins, and also that the large amounts of dark malarial pigment which are present are rather peculiarly distributed. Instead of being most abundant, as is ordinarily the case, according to those who have examined large numbers of malarial livers, at the periphery of the lobules, in this instance the pigment is situated in more or less well-marked zones which correspond nearly to the outer limits of the areas of dilated capillaries. Small amounts of pigment press into the areas of capillary dilatation, and some pigment can be seen in the parts of the lobules in which the capillaries are not dilated, but the great bulk of the pigment is certainly present in the zones described. The portions of the lobules nearest the central veins, and those nearest the peripheries are comparatively free from malarial pigment.

On examination with higher powers, the black and brownish-black malarial pigment is seen to be chiefly included by large makrophagic cells within the liver capillaries, and it is to the accumulation of these cells in the zone previously described, that the peculiar distribution of the pigment as seen with very low powers must be attributed. These large cells in which by far the greater portion of the malarial pigment is contained, vary considerably in size shape and general appearance. The smallest ones correspond in size to the ordinary mononuclear leucocytes, the largest reach the size of giant cells, and are equal in bulk to three four or more times that of the smaller ones. Between these two limits there are many intermediate sizes. Many of the cells have round smooth margins, others are polyhedral, many are oval or ovate in shape. These cells usually contain a single round, or more often an oval vesicular nucleus; sometimes two vesicular nuclei are present. The protoplasm of these cells, when not too much obscured by included substances, can be seen to take a feeble stain in haematoxylin and often to contain larger and smaller vacuole-like

spaces, some of which may represent fat droplets. But as a rule the protoplasm is scarcely visible, owing to the presence of the large accumulations of extraneous substances and structures which have been included within it. It was somewhat puzzling at first to decide as to the exact nature of the different contents of these cells. In thick sections the protoplasm appears to be filled simply with coarse irregular masses of black and blackish-brown malarial pigment, but in thin sections and by various modifications in the staining technique it is possible to distinguish easily a number of different morphological elements. In the largest cells, the protoplasm of which is crowded with black pigment, it can be made out that most of the pigment does not exist in irregular blocks (although some apparently does), but in definite, more or less regularly spherical masses. Often there is an appearance as though a malarial organism, which has been included, had suffered rupture of its capsule, allowing the partial escape of the pigment. From the shrunken malarial capsules (in which the pigment exists usually as a more or less fused and homogeneous mass, rather than as distinct granules as seen in the well preserved organisms) delicate dotted lines of minute pigment particles can be seen running in different directions out into the protoplasm of the phagocytes. Occasionally in these very large cells, much more often in the smaller ones, well developed spherical tertian malarial organisms, with pigment granules arranged in lines in their peripheries and central non-pigmented areas can be seen. The number of included organisms and shrunken capsules (cadavers, corpses, or débris of malarial organisms), is often large. As many as twenty and even thirty were counted in some cells, and doubtless a number of the very large cells, where the bodies lie closely crowded in different planes so that they can be counted only with great difficulty, contain even greater numbers of them. Dark brownish-black pigment in little clumps, resembling that seen near the centers of segmenting tertian organisms, is also observed within these cells, and part of the irregular masses of malarial pigment may represent aggregations of this segmental pigment.

Included in many of these large cells are visible red blood corpuscles, sometimes only one or two, sometimes large numbers of them—true red blood-corpuscle-carrying cells. There are also numerous irregular yellow particles and masses which look like fragments of red corpuscles. On (or in) some of the corpuscles granules of malarial

pigment are seen infected red blood corpuscles (?). In specimens hardened in alcohol, stained with alum-cochineal, and treated with a fresh solution of ferrocyanide of potassium to which a little pure hydrochloric acid had been added, very instructive views of the contents of these makrophages are obtainable. Many of the yellow particles and masses give very definitely the blue haemosiderin reaction, and in this way a much better idea of the number of partially destroyed red blood corpuscles present can be gained. The fully formed intraphagocytic red corpuscles do not as a rule give the haemosiderin reaction, but retain their yellowish tint; some of them indeed are distinctly brassy in appearance, although these brassy corpuscles are by no means so numerous in the liver of this case as in that from a case of an aestivo-autumnal infection. Occasionally, a red disc of full size and normal shape will give the distinct Berlin blue reaction, and at times particles of malarial pigment can be seen lying on such a blue disc. A great many of the fragments of corpuscles do not yield the blue color with the ferrocyanide mixture, so that in the large cells yellow corpuscles, yellow fragments, blue corpuscles and blue fragments lie mixed in varying proportions, along with altered and unaltered malarial parasites and malarial pigment.

As might be expected in cells whose protoplasm is burdened with such large amounts of deutoplasm, the position and shape of the nucleus often deviate widely from the normal. Nearly always placed excentrically, the nucleus is sometimes pushed to the extreme margin or end of the cell, and instead of exhibiting its ordinary oval contour it may assume a stellate or more often a crescentic outline. Sometimes indeed the nucleus is seen to be fragmented, or to be absent altogether, and in such cells the protoplasm has a swollen glassy appearance and is much more refractive than normal.

Besides the malarial organisms and their remains, blood corpuscles and their derivatives, many of these edacious cells contain within their protoplasm still other objects. Thus it is not uncommon to see inside them one or more white blood cells. These included white corpuscles usually have nuclei of the lymphoid type, sometimes they have polymorphous nuclei; or again the two kinds may be present together lying alongside one another in the protoplasm of the same including cell. Sometimes these incorporated white cells contain within their protoplasm well preserved malarial organisms or free pigment. Their

nuclei as a rule stain sharply, and their protoplasm does not appear to be abnormal. At other times the protoplasm of the included cells is more highly refractive than normal, and has a clear glassy look; the nuclei may be fragmented and stain intensely, or they may be entirely necrotic and refuse to take up any of the ordinary nuclear dyes. When the large cell is necrosed (hyaline protoplasm, fragmented or non-staining nucleus) and contains within it white blood corpuscles, these are likely to be leucocytes with polymorphous nuclei.

Finally in the protoplasm of the makrophages (the case being one of general streptococcus infection) cocci occur singly, in chains, or in groups of chains; sometimes the streptococci lie within the protoplasm of included white blood corpuscles.

The makrophages above described lie usually close to the walls of the capillaries but do not appear to have any organic connection with the walls. Sometimes a single one is large enough to practically close the lumen of a capillary. They appear, too, to be lodged quite frequently at the junction of capillaries and to cause obstruction to the flow of blood.

There is an astonishingly large number of well preserved tertian malarial organisms, nearly fully developed, present in the liver. A comparatively small proportion of these apparently uninjured organisms are free in the blood or enclosed simply in red blood corpuscles. The majority of those in the blood-vessels are enclosed within the protoplasm of the large mononuclear leucocytes, from one to six in a cell, and a few within the protoplasm of leucocytes with polymorphous nuclei; although in these latter one rarely sees more than one or two in a cell. As has already been mentioned, a few well preserved malarial parasites are found among the contents of the free makrophages, and as will be pointed out later, occasionally uninjured parasites at the same stage of development as those in the blood are discernible inside the endothelial cells lining the hepatic capillaries. All these organisms appear to be of the same size and present very much the same appearances. They are nearly full grown and ready for segmentation; indeed two definite segmenting bodies (central pigment surrounded by minute oval hyaline bodies) were seen in the blood in one section of the liver. The malarial organisms in alcohol sections in this case studied carefully with the best apparatus are seen to be tolerably regular spheres, consisting of a thin peripheral layer in which

all the pigment is included, and a central more or less spherical mass which does not contain pigment. The brownish-black pigment is not always irregularly distributed in the outer layer, but in favorable specimens it can be seen to have a definite arrangement in lines, with clear spaces between, running like meridians at certain intervals in the directions of the poles. Even in the organisms with ruptured capsules this arrangement can sometimes be made out. The central or usually slightly excentric spherical non-pigmented area stains in certain basic dyes, often quite intensely in methylene blue, only feebly and often not at all in haematoxylin and in aqueous magenta (vide Spleen Plate). The outer layer of the organism in which the lines of pigment run takes no tint with these dyes. The pigment in some organisms tends to accumulate toward one pole, and to retract from the other. This morphology of the organism can best be made out in the larger veins, where the plasmodia are very numerous. The free organisms and infected red blood corpuscles, like the leucocytes, have a tendency to collect along the walls of the veins, where in this case (there being a leucocytosis of considerable degree), together with the leucocytes large phagocytic cells and chains of streptococci, they form masses of considerable size clinging to the venous walls. In some of the veins, however, leucocytes and organisms are fairly evenly distributed among the red corpuscles throughout the lumina of the vessels. Some of the capillaries and smaller veins are crowded with cells malarial parasites and streptococci. The leucocytes (mono- and polynuclear) scarcely ever contain the shrunken remains of the parasites, but besides the well preserved forms there is seen in them an occasional ruptured organism, segmental pigment, and sometimes streptococci. Here and there the nucleus of a white corpuscle is fragmented, and a mononuclear leucocyte may be seen enclosing within its protoplasm a lymphocyte or a leucocyte with a polymorphous nucleus.

The spindle-shaped endothelial cells lining the small veins, and especially those of the hepatic capillaries, present interesting appearances. Many of them contain small fragments of straw-colored blood pigment, and in the protoplasm of some of them malarial pigment, malarial organisms, and the remains of parasites are included. Sometimes streptococci are to be seen within the endothelial cells. The extraneous matter in the endothelial cells does not as a rule greatly increase their bulk, being arranged more or less regularly at the poles

of the nuclei, but now and then endothelial cells are met with which are much swollen, contain large masses of pigment and parasitic remains, and almost obliterate the lumen of the capillary. Occasionally lymphoid cells or polynuclear leucocytes are seen within them. Some of the endothelial cells have hyaline protoplasm similar to that described as occurring in the necrotic makrophages.

In the sections stained with alum cochineal which were afterwards treated with the acid ferrocyanide solution and examined with a low power, the walls of the capillaries (more marked in some regions than in others) are seen to be outlined by delicate blue pigment. Examination with higher powers shows this to be haemosiderin within the protoplasm of the capillary endothelium. Not all of the particles of straw-colored pigment, however, in these cells yield the haemosiderin reaction; while in some of the cells they are all turned blue, in others they all remain yellow, and again cells are seen with blue and yellow particles mixed in varying proportions.

The spaces between the capillary walls and the liver cells are generally exaggerated, more especially towards the centers of the lobules. The cells in these spaces (Kupffer's cells) have acted as phagocytes; they are swollen and exhibit contents analogous to those which characterized the intra-capillary makrophages. The swelling of these cells in some places has been so great as to press the adjacent capillary wall markedly out into the capillary lumen. The rows of liver cells, more especially those about the central vein, are atrophied and are narrow. The cells contain an excess of yellow-brown pigment; the nuclei are more numerous than normal, are shrunken and stain intensely in nuclear dyes. There are very few actual necrotic liver cells to be seen, but now and then one is visible containing a fragmented nucleus, or a nucleus which does not stain at all. The protoplasm of these cells is hyaline and may be invaded by leucocytes with polymorphous nuclei. The liver cells do not contain malarial organisms or pigment. Much of the yellowish-brown pigment within the rows of liver cells yields a blue reaction with Perl's test. In some areas the actual ectasis and liver cell atrophy is extreme. In those where the changes in the liver cells are the same the capillaries appear to be collapsed and the number of nuclei present is striking. The liver cells of the peripheries of the lobule are large and some of them contain giant nuclei. In the connective tissue of the portal spaces

there are some large cells filled with clumps of dark malarial pigment. There is a slight increase in the number of lymphoid cells in these spaces.

Spleen.—The comparatively small size of the spleen is due to the existence of chronic interstitial changes. On microscopic examination the capsule and trabeculae generally are found to be much thickened, and there is thickening and fibrous transformation of the reticulum of the pulp. The spleen, however, also shows evidences of less chronic lesions. The spleen-pulp is hyperaemic and there is a marked increase in the number of colorless cells in the pulp-cords and within the splenic veins and capillaries. A goodly number of red blood-corpuscle-carrying cells can be made out. While some of these cells contain only red blood corpuscles as inclusions, in others are also seen malarial parasites and pigment together with some nucleated white cells.

There are large numbers of malarial parasites in the large and small splenic blood-vessels, exactly similar to those described in the liver. Some are free in the blood, or lie on or in infected red corpuscles; the majority of well preserved organisms are contained within the protoplasm of cells; there are from one to six in each of the cells, which are of the size and general appearance of large mononuclear leucocytes. As a rule the nuclei of these cells stain well, but occasionally they do not take the dyes at all. A few well preserved organisms and some free brownish-black (segmental?) pigment are to be seen within the leucocytes with polymorphous nuclei. The nuclei of a few of the mononuclear and polynuclear leucocytes in the splenic capillaries are fragmented, the chromatin being broken up into deeply staining masses of varying sizes.

In addition to these cells there are in the splenic capillaries, veins and pulp, many makrophages, large usually mononuclear cells, whose swollen protoplasm is crowded with masses of malarial pigment, the shrunken remains of malarial organisms, organisms with ruptured capsules, and occasionally with one or several well preserved organisms in the same stage of development as those free in the blood. These cells contain in addition many red blood corpuscles and fragments of red corpuscles, part of which yield the haemosiderin reaction. On some of the included red corpuscles particles of fine malarial pigment are visible, suggesting that these corpuscles when received

into the phagocyte were infected with malarial parasites. These makrophages may contain, like those in the liver, white cells, and some of these included cells may contain other cells, so that one sees cell within cell within cell, and as the protoplasm of all three may contain extraneous substances, one may speak of phagocyte within phagocyte within phagocyte. The nuclei and protoplasm of including and included cells vary in appearance—sometimes the former, sometimes the latter show evidences of degeneration or necrosis. Streptococci are very abundant throughout the spleen; they appear in single chains and in masses of chains. They are especially well defined in the sections stained with methylene blue and eosin, and in those prepared according to Weigert's method for the differentiation of fibrin, bacteria and hyaline. They can often be seen enclosed within the protoplasm of cells, mononuclear and polynuclear leucocytes, intravascular makrophages, and endothelial cells. Some of the small veins and splenic capillaries are actually thrombosed with masses of streptococci, white corpuscles, malarial organisms and phagocytes, matted together with filaments of fibrin.

The endothelial cells in the spleen, like those of the liver, are swollen and contain within their protoplasm blood pigment, part of which has been transformed into haemosiderin. A few of them also contain malarial organisms, cadavers of parasites, and free fine and coarse malarial pigment; streptococci may be seen within some of them.

A certain number of the large makrophages within the splenic pulp are arranged in groups, and present a peculiar appearance. The cells are much swollen, and besides the ordinary contents of collapsed organisms etc., large areas of the swollen protoplasm show yellowish-brown pigment arranged in dotted lines ramifying through the protoplasm, which is often hyaline, so that we have something which looks like tangled masses of pigment lines, often over-lying and hiding the nucleus from view, and enclosing minute areas of hyaline protoplasm within the felt-work (*vide* Plate VI). These lines of pigment often appear to run out from the pigment masses enclosed within the cells. The pigment in these lines when in focus is seen to be dark brownish-yellow in color, while that out of focus may be of a pale straw color. The malpighian corpuscles of the spleen are somewhat swollen and are almost entirely free from coarse malarial pigment. On close

examination, however, fine malarial pigment, yellowish-brown in color, arranged often in lines, and not enclosed within cells, can be made out in many of the malpighian bodies lying in the interspaces between the lymphoid cells.

The Kidney.—An examination of many glomeruli shows considerable variation in the size of the capsular spaces. While in some instances the glomerulus almost completely fills out Bowman's capsule, the space being a mere chink, in others the latter is equal in size to one-third of the whole capsule. The space is not always empty but may contain coagulated albumin, red blood corpuscles and shadows, or a few mononuclear cells (desquamated epithelium). The fibrous capsules are not thickened except occasionally where an atrophied glomerulus is visible. Frequently just outside the capsule of Bowman a narrow clear space can be made out, and this may contain a few cells, chiefly polynuclear leucocytes, or even be crowded with them. In many of the capsules the capsular epithelium is evidently proliferated, the whole inside of the space being lined by nuclei with intensely staining chromatin. The glomerular capillaries vary in their size and contents; some of them are empty, others are distended. Occasionally one is seen to be plugged with streptococci. The number of white corpuscles within the glomerular capillaries also varies; they are very irregularly distributed; in some glomeruli scarcely any are present; in others one two or more of the glomerular capillaries may be packed full of polynuclear leucocytes. In a section stained in methylene blue, a capillary is visible plugged at one point with streptococci and crowded throughout the rest of its extent with leucocytes with polymorphous nuclei,—reminding one forcibly of the appearance of the capillary glass tubes in an experiment in positive chemotaxis. On the other hand masses of cocci may be seen with no neighboring leucocytic accumulation. The nuclei of the polynuclear leucocytes vary in appearance; some stain sharply and take on the ordinary forms; others stain less sharply, have a blurred look and assume bizarre shapes. The protoplasm of the polynuclear leucocytes frequently contains granules or minute clumps of granules of malarial pigment, occasionally a well-formed parasite or short chains of cocci. There is some malarial pigment in the glomeruli contained within the protoplasm of mononuclear cells. The majority of the malarial parasites in the glomerular capillaries are outside nucleated cells.

Here and there in specimens stained with aqueous magenta a giant spindle-shaped nucleus is visible.

The lumina of the convoluted tubules are for the most part wide and are lined with rather low cubical epithelium. There are a few areas of dilated tubules, in which the lining epithelium is flattened so as to resemble endothelium. The nuclei of the epithelial cells as a rule stain normally, although in some swollen cells they stain feebly, and in some tubules the nuclei are shrunken and the chromatin stains more intensely than normally.

Many of the convoluted tubules and collecting tubules contain hyaline casts; and hyaline droplets are visible within the swollen lining epithelial cells. These droplets, both the finer and the coarser, and the upper portions of the hyaline casts stain intensely in Weigert's fibrin stain. Occasionally desquamated epithelial cells and a few red blood corpuscles and round yellowish striped urinary concrements are to be seen within the lumina of the tubes.

The intertubular capillaries contain enormous numbers of streptococci (methylene-blue, Weigert's fibrin stain). Many of them are dilated and completely plugged with cocci, and sometimes chains of cocci are visible in narrow pericapillary spaces. As in the glomerular vessels, some of the intertubular capillaries are crowded with leucocytes. Some of the small veins in the cortex are actually thrombosed with masses of streptococci, large numbers of malarial parasites, white corpuscles (some of which are necrotic), and pigment clumps. No bacteria other than streptococci are present anywhere in the kidney.

In the interstitial tissue of the kidney there is a slight but evident increase in the number of cells of the lymphoid type. There are small nodal masses of smaller and larger round cells, usually with but little perinuclear protoplasm, many of them with fragmented nuclei. These minute nodes may contain, besides lymphoid cells, single polynuclear leucocytes or epithelioid cells.

Sections of the kidney treated with ferrocyanide of potassium and hydrochloric acid show an almost entire absence of cells containing haemosiderin. Here and there, however, a little is visible within the protoplasm of the endothelium of the vessels.

The infarcted areas of the kidney present the lesions ordinarily seen under these circumstances—anaemic necrosis and neighboring reaction. The whole of the necrotic area—glomeruli, tubules, blood-

vessels, interstitial tissue—refuses to stain in the ordinary nuclear dyes, and has an increased affinity for eosin. The only nuclei which stain are those of polynuclear leucocytes which have invaded the interstitial tissue everywhere, and are accumulated in large numbers at the margins of the infarcted areas, and in the neighboring dilated blood-vessels. There is extensive nuclear fragmentation in these polynuclear leucocytes, and the most varied distortion-processes (abschnürungsvorgänge) of their nuclei are visible. Many of the blood-vessels at the apices and in the peripheries of these infarctions are thrombosed with streptococci, enormous numbers of malarial organisms, over 100 of which were counted inside the lumen of one vessel, and white cells. Small bits of the kidney hardened in Flemming's stronger solution and stained with aqueous magenta yield very instructive sections. Fine fat droplets are visible in the glomeruli and in the epithelium lining the capsular spaces. The convoluted tubules are not extensively fatty; some are entirely free from fat droplets, others show numerous smaller and larger droplets, especially at the proximal ends of the lining epithelial cells. Fine fat droplets are also visible in the protoplasm of some of the leucocytes in the vessels, and also in the smooth muscle fibres of the arteries. The desquamated epithelial cells within the lumina of the tubules contain numerous rather coarse fat droplets. The cells of the convoluted tubules in sections prepared in this way are seen to be finely granular and the hyaline degeneration of the protoplasm is well shown. Many of them contain large vacuole-like spaces which sometimes displace the nuclei. In some of the tubes free red blood corpuscles, polynuclear leucocytes, and malarial organisms are visible. The last named are sometimes free or lie on red blood corpuscles, sometimes they are enclosed within cells. They are to be seen in both polynuclear and mononuclear cells within the lumina of the convoluted tubules. In one tubule, besides numerous red blood corpuscles and shadows, four free well-formed malarial organisms and a mononuclear cell containing within its protoplasm five malarial organisms of the same stage of development can be made out. Pictures such as these were seen too often to be accounted for by technical accidents. Occasionally red corpuscles malarial parasites and white cells are visible within the glomerular capsular spaces.

The Bone Marrow.—The malarial parasites in the marrow are for the most part enclosed within mononuclear cells; numerous makro-

phages are here present with contents very similar to those described for these cells in the spleen. Streptococci are numerous, some free in blood-vessels others enclosed within white cells. The endothelial cells contain blood pigment at the poles of the nuclei—part of which yields the blue reaction. There is an increase in the number of the white cells in the marrow, and a considerable number of nuclei are fragmented. Nucleated red blood corpuscles are abundant, as are also degenerated red corpuscles, occurring singly and in clumps. Some of the streptococci in sections treated with ferrocyanide of potassium and hydrochloric acid yield a sharp blue reaction, so that the chains of cocci look as though stained in methylene blue. The same result was obtained with some of the cocci in the spleen.

The Adrenal Glands.—In the literature, the lesions of the suprarenal capsules in malaria have not received the attention which the findings in this case would show that they deserve. The arteries and veins of the capsule are wide and contain many malarial organisms as well as single chains and masses of streptococci; the lumina of some of the veins are completely filled with accumulated leucocytes (mononuclear and polynuclear), malarial parasites in and outside of red corpuscles and streptococci. A few makrophages are also present in the veins of the capsule. There are irregular areas of vascular dilatation throughout the sections. The vessels of the zona glomerulosa are generally distended, as are those of the medulla; in the zona fasciculata and in the zona reticularis the capillary and venous dilatation occurs in areas. It will be remembered that in the liver the rows of liver cells had undergone an extent of atrophy corresponding to that of the capillary dilatation; similarly here in the area of capillary ectasis the adrenal cells are small.

Malarial parasites are numerous in all the distended vessels; many of them are obviously within red corpuscles, a large number are enclosed within the protoplasm of mononuclear leucocytes—from one to four in a cell. Polynuclear leucocytes are numerous; they often contain segmental pigment and occasionally a malarial organism. The makrophages, with contents like those in the liver and spleen, are present in considerable numbers in the adrenal capillaries, being somewhat irregularly distributed through the cortex and medulla; they are perhaps most abundant in the outer portion of the zona fasciculata, and fewest in the zona glomerulosa which is tolerably free from pigment

masses when looked at with very low powers (8 and 16 diameters). The endothelial cells are phagocytic here as in the liver, their nuclei are large and vesicular, their protoplasmic contents quite similar to those of the intra-capillary makrophages, except that they consist rather more of blood pigment and less of malarial pigment, the foreign substances being arranged mainly at the poles of the nuclei. Outside the capillary walls, between them and the adrenal cells of the zona fasciculata, here and there mononuclear makrophages are visible, not unlike the phagocytic cells of Kupffer in the liver. It is possible to make out, too, that a few of the true adrenal cells in places contain within them malarial pigment and infected corpuscles—a fact which should not surprise us when we consider the close relation of certain parts of the adrenal parenchyma to the veins which has been recently demonstrated by Manasse.

In places there are capillary thrombi of pure streptococci, and cocci in single chains or in clumps are irregularly distributed in the capillary districts. Here and there in sections stained in methylene blue they are visible inside of cells (leucocytes, makrophages, endothelium of capillaries).

Many of the adrenal cells, often in foci, are swollen, vacuolated, and fatty, and show fragmented nuclei. The chromatolytic changes are best seen in sections stained in aqueous magenta.

The Lungs.—The pulmonary and pleural veins are widely distended, and in them enormous numbers of malarial organisms are visible. The parasites are chiefly in red blood corpuscles, but many of them have been included, often along with streptococci, by white cells (chiefly mononuclear, but also polynuclear). The white corpuscles tend to accumulate in groups, and they, together with infected red corpuscles, makrophages, free malarial parasites, and masses of streptococci, are frequently massed near the walls of the vessels. The parasites are present, too, in considerable numbers in the pulmonary capillaries and in branches of the pulmonary artery. Lesions associated with coal pigmentation, and moderate emphysema are present, otherwise the lungs show no marked alterations. No other tissues from this case were preserved for microscopic examination.

The fact that the malarial infection was not recognized during life, the enormous number of parasites, the extensive phagocytic processes,

and particularly the mixed infection and the lesions in the kidneys make this case one of more than ordinary interest.

It may not be out of place here to make a few general remarks concerning the bacterial infections and protozoan invasions which may be concurrent with malaria.

In the clinical section of this fasciculus (Report by Thayer and Hewetson) the occurrence of multiple malarial infections is considered, and the fact that an individual may be infected at the same time with different groups or generations of the same organism or of organisms of different types, is found to account for many of the manifold manifestations of the disease which may be met with. But in addition to a knowledge of such multiple *malarial* infections, a consideration of the possibility of the co-existence with malaria of other protozoan infections, and of certain bacterial diseases, both local and general, throws some light upon certain problems connected with malaria which have been heretofore obscure.

Concerning protozoan infections concurrent with malaria little is known. In the Johns Hopkins Hospital one case of malaria has been met with in which there was an associated dysentery due to the amoeba coli.

The bacterial infections which may be associated with malaria are numerous. In the first place the occurrence of a complicating pneumonia in malaria, which led years ago to so much polemical literature, is now satisfactorily explained. The pneumonias which were believed to be due to a malarial poison are now known to be due not to this cause, but to an associated bacterial infection. Manson and others have described forms of pneumonia peculiar to the disease when occurring in conjunction with malaria, and it was believed that this pneumonia was particularly prone to terminate fatally. The review of the whole subject by W. T. Howard in 1859 had an important influence, and still merits careful reading. Osler opposed the view that the pneumonia in malaria was special to the latter disease. Finally Bignami, Marchiafava and Guarnieri have described cases which came to autopsy, at which careful bacteriological examinations were made, by which it was proved that the croupous pneumonias of malaria, like other cases of croupous pneumonia, are due to infection with the micrococcus lanceolatus.

In addition to croupous pneumonia, bronchitis and broncho-pneumonia are frequent complications of malaria, and probably may be due to any one of the pyogenic organisms. The much disputed typho-malarial fever, by the light of our present knowledge, presents no difficulties. It is now well established that the majority of cases of so-called typho-malarial fever and typho-intermittent fever are really genuine cases of typhoid fever. That a typhoid infection may co-exist with an invasion by the malarial parasites is indeed certain; upon this point the cases reported by Osler and by Gilman Thompson have left no room for doubt.

The rare cases in which an acute ulcerative endocarditis is seen in conjunction with malaria, now that the etiology of the endocarditides is better understood, will probably turn out to be examples of mixed bacterial and malarial infection.

Erysipelas sometimes co-exists with malaria; at least one such case has been met with in the wards of this hospital.

Of the predisposition to dysentery depending upon alterations in the nutrition of the mucous membrane lining the alimentary canal we have already spoken. The chances of bacterial ingress and the possibilities of a general septic infection in such cases is obvious. Cases of general streptococcus infection, such as the one described under the head of Case D, are undoubtedly rare.

VI.

ON THE UNEQUAL DISTRIBUTION OF THE PARASITES IN THE BODY IN MALARIAL INFECTION.

The recognition of the existence of pigment in the blood and in the various internal organs of patients suffering from malarial infection antedated by many years the discovery of the organisms of malaria by Laveran in 1880. But the studies of these earlier observers went beyond the recognition of its mere existence, since it was noted by quite a number of them that the pigment was not equally distributed throughout the body. Thus, in the well known case of Meckel in an insane patient, in whom the spleen was enlarged and deeply pigmented, particles of pigment were found in various parts

of the body, and it was suggested that these had been swept out of the spleen by the blood and carried by the current to the other organs.

Virchow in 1848, in describing the melanaemia of a malarial patient, speaks of the large accumulation of pigment in the spleen and liver, and at the same time notes the finding of this substance enclosed in the cells in the blood of the heart.

Planer suggested that the comatose and apoplectic forms of severe malaria might be explained by the lodgment of emboli of pigment in the brain capillaries. Frerichs attributed the atrophy of the parenchyma of the liver, observed in some of the cases, to obstruction in the liver capillaries.

Since the discovery of the malarial parasite, those who have had opportunities of studying specimens of the fresh blood from a large number of cases of malarial infection, have not only been able to recognize certain distinct types of parasites as belonging to the various clinical forms of the disease, but have also been able to add some curious facts relative to the distribution of the organisms in the blood and organs. Councilman, Celli and Marchiafava and others observed in cases of the comatose form of pernicious malaria, the frequent occurrence in the brain of capillaries plugged with parasites. Councilman, too, early pointed out that the number of crescentic forms of the organism in the circulating blood was seldom large, but that their tendency was to accumulate in considerable numbers in the spleen.

The question of the unequal distribution of the parasites in the body assumes especial importance when considered in connection with the three main types of the malarial organisms. Without entering into a detailed description of the individual observations which have led up to our knowledge of the subject as it may at present be formulated, the broad statement may be made that in infections with quartan parasites one sees the most equal distribution of the parasites throughout the blood and various organs, and that in infections with parasites of the aestivo-autumnal variety the most unequal distribution is encountered. In infection with parasites of the tertian type, the character of the distribution may be said to stand between that of the quartan and that of the aestivo-autumnal infections, approaching perhaps a little more closely to the former.

In the quartan fevers the parasites are nearly always to be seen in numbers in the blood in any of the peripheral parts, and during the

paroxysm many segmenting bodies, although they show a decided tendency to accumulate in the organs, are observable in the blood taken from the finger-tip or from the lobule of the ear. Indeed, so regular is the distribution of the organisms throughout the body in this type of malarial fever, that a tolerably definite estimate of the severity of the infection can be made simply from the number of organisms to be seen in the fresh blood slide.

The parasites in tertian fever, although usually quite abundant in the circulating blood, show decidedly a more marked tendency to accumulate in the internal organs, such as the spleen, the liver, and the marrow of the bones. This is notably true at the time of the paroxysms when the segmenting organisms, although usually still present in severe infections in considerable numbers in the peripheral blood, are for the most part retained in the internal organs and especially in the spleen.

But it is in the infections with the aestivo-autumnal parasites, infections which include the majority of comatose and other pernicious cases, that the most curious and marked variations in the distribution of the parasites are to be met with, and the findings in these cases have gone far to make clear the diverse and startling clinical manifestations to which these infections may give rise. It is in these cases more particularly that pathologists, through observations at post-mortem examinations, have been able to make important contributions to the understanding of a disease, the main progress in which is undoubtedly due to the work of the clinical investigators.

In the aestivo-autumnal infections, the number of organisms in the blood circulating in the peripheral parts afford as a rule very insufficient data upon which to base an idea of the severity of the infection. As clinical experience has taught, numerous slides prepared from the peripheral blood may show very few organisms, and these often of the type most difficult to recognize, while in a drop of blood taken from the spleen quite a large number of the parasites may often be made out with ease.

The occurrence of segmenting organisms in the peripheral blood is a phenomenon of extreme rarity in aestivo-autumnal infections.

Golgi, Bignami and others have pointed out the fact, which can easily be substantiated by careful observation, that in aestivo-autumnal malaria the distribution of the parasites may vary in different parts

of the same organ. Thus in the fluid obtained from tapping the spleen in different regions, the number of organisms is prone to vary considerably, and in sections of the spleen, liver, and other organs, it is not difficult to convince one's self of the disparity in the number of organisms in different vascular territories.

Among the most interesting and most important of the local accumulations of the parasites is the formation of parasitic thrombi. In the comatose forms of malarial fever it is not uncommon to find capillaries and small veins in the brain distended with masses of malarial parasites of the aestivo-autumnal variety, which probably are identical with the so-called pigment thrombi of the early observers. These may be pigmented organisms and segmenting forms, or according to Bignami, the thrombi may sometimes be made up of the small pale non-pigmented bodies first described by Marchiafava and Celli.

The profound disturbances of nutrition necessarily consequent upon such a condition, which is not unfrequently accompanied by necrosis, would alone, without a consideration of the effects of the toxines which the parasites produce, suffice to explain many of the clinical phenomena referable to intra-cranial involvement.

It is not to be supposed that in any given case, all the capillaries are alike affected. As a matter of fact, while two or three may be completely filled with parasites, their neighbors for some distance around may be almost or entirely free from them. When we consider the many variations possible in the implication of the capillaries in any organ, the diversity of the disturbances of the cerebral functions observable clinically becomes easily understandable. It is not difficult to conceive that herein may lie the key to the transitory aphasias, the variation in degree extent or duration of the paralyses, or of the mental irregularities occasionally noticeable in the severer forms of aestivo-autumnal fever; and when, along with other things, we remember that comparatively limited disturbances of the circulation in certain of the vital centres, such as the medulla,[1] suffice at times to cause sudden death, it is not surprising that the type of malarial infection which is associated with the possible occurrence of the capillary thrombi of parasites should have won for itself the title of *malaria perniciosa*.

[1] Marchiafava has recorded a case in which he noticed a special localization of the parasites in the neighborhood of the bulbar nuclei.

In describing the findings in Case B, attention was directed to the accumulations of parasites within the capillaries and small veins of the mucous membrane of the stomach, and to the necroses on the surface of the mucosa, which could fairly be attributed to the disturbances in the nutrition of the part. There are numerous instances in the literature in which, after death, a similar condition has been found in the vessels of the mucous membrane of the intestines, the patient during life having shown the symptoms of profound intestinal disturbance and even of an acute dysentery. The cases are so characteristic as to be worthy of a definite place in nosology and the names *malaria perniciosa cholerica*, and *malaria perniciosa algida* have been suggested to describe these forms.

It would probably be fair, arguing by analogy, to assume—and many observations would seem to confirm the view—that the occurrence of similar parasitic thrombi in other organs of the body may lead to alterations in nutrition and function which materially influence the course and progress of the disease.

Any attempt to explain the reasons for this unequal distribution is beset with many difficulties. While the slow circulation and the calibre of the vessels in certain organs certainly play a part, yet the distribution of parasites in all forms of malaria is, as we have seen, very different from that of inert substances when introduced into the circulating blood. Undoubtedly, many factors have to be considered, and how far any one or more are concerned in a given case is difficult to determine.

In another section, in which phagocytosis is dealt with, the localization of the parasites in certain organs inside of cells will be more fully commented upon. As Bignami suggests, the activity or inactivity of the phagocytes of a certain organ may have an important influence upon the distribution. He lays stress, too, upon the fact that the parasites are usually endoglobular, and that infected red corpuscles, from loss of elasticity or other physical alteration, may be impeded in their progress and tend to accumulate in the viscera in which the circulation is slowed. It is certainly true that in the abdominal area where the slowness of the circulation is accentuated in malaria, owing to obstruction in the liver by endothelial swelling or accumulation of makrophages within the capillaries, the massing of the parasites is ordinarily marked, while in organs in which the

circulation is most active, very few parasites as a rule are present. That the parasites and infected red cells collect along with the white corpuscles on the inner walls of the larger veins is a fact which could be confirmed in many of the specimens from the autopsies of this report, but as to the explanation of this phenomenon nothing is as yet certainly known.

As regards the tendency in the pernicious cases to the formation of thrombi composed of parasites in certain vascular territories our knowledge is most at fault. The idea that certain capillaries become plugged with makrophages, and that in the dilated vessel behind the point of obstruction the corpuscles in the stagnant blood all become infected, will not suffice for the explanation of all the instances. That vaso-motor influences in certain vascular areas play, as Bignami suggests, an important rôle seems plausible, especially in cases of the pernicious algid form.

It is perhaps not impossible to learn something from the analogies observable in tumor metastases, in bacterial infections or even in simple intoxications. It has long been a puzzle to pathologists why in cases of general sarcomatosis or carcinosis, where the distribution is through the general circulating blood, that in some cases one organ or set of organs, in other cases other portions of the viscera have remained free or nearly free from metastatic growths.

Again as regards the general bacterial infections those who have as a matter of routine made bacteriological investigations of all the organs at a number of autopsies, will be familiar with the fact that in such cases the bacteria even at perfectly fresh autopsies are by no means equally apportioned through the blood and viscera. Indeed, it is a common occurrence to find that one or two of the organs contain relatively many fewer bacteria than the others. But that there is little regularity in the inequality of distribution is shown by the study of numerous cases of general infection with the same micro-organism, *e. g.* the streptococcus. Whereas the plate cultures made from the spleen in one case of septicaemia may be closely crowded with colonies and those from the liver contain only a few, in another instance the conditions may be exactly the reverse. Every one is acquainted with the relative immunity of some organs in acute general miliary tuberculosis, an immunity which can be made out often from the naked eye appearances alone, although it is often difficult to decide whether

the irregularity is an expression of a primary inequality of distribution, or to differences in the resistance offered to the local multiplication of the distributed organisms or again to the different effect which they produce on the tissues in which they develop.

And after all when we consider the fact that in malaria we have to deal with a crude mixture of malarial parasites, blood corpuscles and blood plasma, the anomalous distribution of the parasites, as ascertained by post-mortem examinations, should be much less difficult to account for than the unequal diffusion through the organs of substances which are dissolved in the blood, a phenomenon which of late has attracted considerable attention. It is scarcely necessary to call to mind that normally certain chemical bodies are removed from the circulating fluid by various glands to serve in the manufacture of secretions. Again, the discovery of the accumulation of poisons in certain organs, *e. g.*, morphine in the liver, spleen and bone marrow, and certain other vegetable poisons in the liver, for purposes of elimination or neutralization must be reckoned among the observations which help to make general toxicology interesting. In the domain of bacterial toxicology, Welch and Flexner have demonstrated the occurrence of definite focal lesions in the tissues of the body produced by a soluble poison circulating in the blood, a finding which is scarcely compatible with any assumption other than that the dissolved poisons are not evenly distributed even in the individual organs.

Now that the vital characteristics and varying sensibilities of unicellular organisms are becoming better known and appreciated, we have learned to have more respect for a cell as an individual, and the conclusion that this unequal distribution is dependent upon a complexity of factors will not excite surprise. If it be borne in mind that the parasites are constantly exercising their metabolic functions; if the question of food relations and that of the influence of excretory substances from the parasites together with the alterations in the metabolism of the cells of the various tissues (*e. g.*, those dependent upon the destruction of red corpuscles) be taken into account, it will be seen that the whole problem of anomalous distribution, as influenced by factors incident to the parasite and factors incident to the cells, may become extremely complicated, and that we can scarcely hope in the very near future that all the intricacies, whether they be due simply to mechanical factors or to those which we must regard as the outcome of vital influences, will be explained.

VII.

ON PHAGOCYTOSIS IN MALARIA.

Among those who have insisted upon the importance of the part played in malaria by the so-called phagocytes are Metschnikoff, Guarnieri, Bignami, Laveran, Dock, and especially Golgi and Bastianelli. As has been said above, a study of the literature shows that malarial pigment had been observed in the cells of the different organs and in the white cells floating in the blood long before the parasitic nature of the disease had been established, and a great deal of this pigment is now known to be within the bodies of the parasites.

The inclusion of the malarial pigment and of the malarial parasites within white cells, fixed or floating, occurs in all cases of malaria, although the extent of the process varies somewhat in different individuals, and with the different varieties of malarial infection. The microscopic examination of the cases which came to autopsy here, showed that the reports of other observers on this subject had not been exaggerated.

The cells actively concerned in phagocytosis are not all of one kind. Besides different varieties of leucocytes, certain of the fixed cells of the organs, the endothelial cells generally, but especially those in the liver and spleen, the cells of Kuppfer in the former, and the cells of the pulp-cords in the latter, take no unimportant part in the process.

The contents of these different phagocytic cells vary also. Speaking generally, it may be stated that the cells concerned may enclose within their bodies any of the following: (1) red blood corpuscles, many of them altered, others apparently little changed; (2) fragments of red corpuscles; (3) masses of haemosiderin (probably formed within the cells); (4) malarial parasites, in different phases of the developmental cycle, many of them endoglobular, many of them degenerated or going to pieces; (5) malarial pigment, especially the central pigment clumps from segmenting parasites; and (6) white cells both mononuclear and polynuclear. A phagocytic cell is sometimes seen to contain all of these structures at one time, but this is not a common observation. Special names have been assigned to the phagocytic cells in accordance

with the character of their contents—thus the leucocytes containing malarial pigment are spoken of as "pigmentiferous" or "melaniferous;" the cells containing red corpuscles as "globuliferous;" while those containing parasites are known as "amoebiferous" cells. Following this nomenclature the cells containing other phagocytes might be called "phagocytiferous," just as those containing white corpuscles have been spoken of as "leucocytiferous," but it is doubtful if much is to be gained by any extension of this awkward terminology.

The different forms of phagocytes seen in our cases have been fully described in the protocols of the microscopic examinations, and need not be further considered here. One point to which attention may perhaps be directed is the manifest division of labor which exists among the various forms of phagocytic cells. While any one of the varieties seemed capable of taking up at times almost any of the substances above mentioned, yet when the tissues are studied carefully it is easy to make out that they do not all contain these various substances in the same proportions, but that as a matter of fact the white corpuscles and endothelial cells appear to possess more or less definite elective affinities. For example, in Case D while the mononuclear leucocytes contained the majority of well preserved parasites, the polynuclear leucocytes showed a preponderance of the segmental pigment; while the makrophages in the spleen and liver contained large numbers of infected and otherwise altered red corpuscles and remains of malarial parasites, the endothelial cells of the spleen and liver often contained blood pigment to the exclusion of all other visible kinds of foreign material. Laveran, Councilman, and Golgi early noted that leucocytes carrying pigment were most abundant in the blood just after the onset of a paroxysm, and suggested that the increased number of pigmented corpuscles might depend upon the setting free of large quantities of pigment during segmentation. Supposing that there might exist a periodicity to the phagocytosis corresponding more or less nearly to the developmental cycle of the parasite, Golgi made certain studies, the result of which convinced him that the idea had a basis in fact. From these investigations he concluded that the white cells in the organs, particularly in the spleen, played even a more active part in phagocytosis than those in the blood, a conclusion which had also been reached by Metschnikoff from the study of sections of the spleen and liver in malaria. Basti-

anelli found further in his extensive study of the leucocytes in malaria a marked increase in the number of pigmented leucocytes in certain cases at the beginning of the febrile paroxysm, but as might have been expected saw less evidence of periodicity in the aestivo-autumnal cases. He seems inclined to attribute the major share of the phagocytic work to the large mononuclear elements. The same writer confirmed the observations of Bignami concerning the degeneration of phagocytic leucocytes and suggests that the diminution in the number of leucocytes in malaria may be attributed to this cause. John S. Billings, Jr., who made accurate counts of the total number of leucocytes, and also differential counts of the various forms of white corpuscles by Ehrlich's methods of color analysis, before, during and after the paroxysms, found that in certain cases there was always a diminution in the number of leucocytes during the febrile paroxysm. In a chart accompanying his article in which a composite curve of the temperature is compared with a similar one representing the number of white corpuscles, it is evident that, while just before the chill the number of white cells to the cubic millimetre is approximately normal, there is a steady though not very marked increase in the number for from two to three hours until a maximum is reached, after which there is a relatively sharp and steady decline corresponding with the fall in temperature until a minimum is reached which is considerably below the normal. As to the color analysis of the leucocytes, Bastianelli found a decrease in the leucocytes with polymorphous nuclei with an increase in the large and small mononuclear elements. According to Billings a decrease in the polynuclear and an increase in the large mononuclear cells is constant, while there is no regularity as to the percentage of small mononuclears and eosinophiles.

The clinical observations just referred to are of considerable interest in connection with the appearances in the organs at autopsy, and it is interesting too to compare the examples of phagocytosis observable in the blood drawn from the circulation during life (*vide* a report by Thayer and Hewetson) with those seen in the sections from the cases now reported. According to these observers it is extremely rare to notice any active phagocytic tendencies on the part of the mononuclear elements to parasites in blood taken from the finger or ear, although it is by no means uncommon to see a leucocyte with a polymorphous nucleus gradually enclose a flagellating parasite or a fragmented ex-

tra-cellular body in the fresh blood slide. It will have been seen above, however, that in the blood in the sections from Case D the majority of parasites are enclosed within large mononuclear leucocytes. It has been stated, too, that neither the parasites nor the including cells necessarily show evidences of degeneration. The question naturally arises, "Could the enclosing of the parasites by the large mononuclear leucocytes in this case have been a post-mortem phenomenon?" Dock has shown that the malarial parasites are arrested in their development soon after the death of the patient, and it is of course quite conceivable, though in my opinion it is improbable, that certain changes occurring in the parasites inside the body after death rendered them suitable to be taken up by the large white cells. It is unfortunate that in this case no blood examination was made during life. So many of the large mononuclear leucocytes as seen in the sections contain parasites within their protoplasm, that had the ingestion occurred ante-mortem it could scarcely have been overlooked upon examination of the fresh blood.

The original statement of Metschnikoff that the endothelial cells of the capillaries, especially in the liver, take up the parasites has been questioned by some observers. The tissues from the autopsies here reported unquestionably confirm Metschnikoff's statement, though as we have said, the endothelial cells are much more prone to take up the remains of altered blood corpuscles than to include malarial pigment or the parasites.

The red blood-corpuscle-carrying cells and the huge phagocytic cells of the spleen attract special attention. When one studies sections of the spleen and sees the enormous number of these makrophages, the accumulations of fragmented red corpuscles, the necroses, and the dilatation of the blood-vessels in this organ, he has not to go far to seek an explanation for its enlargement in malarial infection. The number of makrophages which are carried from the spleen through the splenic vein into the liver cannot fail to be of considerable significance. As was pointed out in the description of the tissues they frequently appear to occlude the liver capillaries, and to offer a serious impediment to the onflow of blood. Guarnieri thought that this obstruction in the liver capillaries might account, in part at least, for the enlargement of the spleen (venous stasis), and suggested that possibly the pernicious forms of malaria might depend upon an in-

toxication due to the disturbance of the functions of the liver—a view which he has doubtless given up long before now.

The question may fairly be asked, "What becomes of these migrated spleen cells loaded down with ingested material?" If we can judge by an examination of the tissues elsewhere, there are comparatively few carried through the liver into the general circulation, unless indeed the greater number of them have been diminished in size, and have gotten rid of some of their contents so that they were able to pass through. This they could do in part through cellular digestion. It seems to me, however, that, carrying as they do, besides malarial parasites and malarial pigment, considerable quantities of haemoglobin and of blood coloring matter already altered within the cell so as to give the blue iron reaction, these cells may exercise an important function in carrying to the liver the materials for the manufacture of bile. It is not inconceivable that these makrophages lying in direct contact with the endothelium of the hepatic capillaries could yield up a portion or all of their contents to the latter. It would indeed be interesting if it should turn out that the blood pigment in the makrophages, in the vascular endothelium, and in Kupffer's cells stood in some such direct relation to the bile manufactured by the liver cells. Certainly the liver cells must draw their iron substances from the blood, and from what we know now-a-days of the varied capacities of white blood corpuscles and of endothelial cells, the occurrence of some such interchange of raw materials as has been hinted at would not be surprising. It may be that the study of pathological accentuation of the bile-making activities of the liver may throw light in the future on the still obscure physiological processes which go on in this organ.[1] The metabolic processes of the body tend towards economy; the re-making of materials by different organs is common, the refuse from one organ often being essential for the nutrition and well being of certain of the others (law of Treviranus); and this being so, the relations of phagocytosis to the nutritional activities of the body form an interesting topic for investigation.

The makrophages in the vessels of the mucous membrane of the alimentary tract have been mentioned in connection with Case A. Dock describes finding one similar cell in one of his cases. It is

[1] Compare the researches of Dr. William Hunter, *On the Physiology and Pathology of Blood Destruction*, Brit. Med. Jour., 1892, ii, p. 1159 and 1223.

generally stated that eosinophilic cells never act as phagocytes in malaria. The late Dr. Oppenheimer, however, recently showed me in a slide of fresh blood a makrophage which contained large, round, yellowish, refractive granules which closely resembled the ordinary eosinophilic granulation; the cell enclosed several infected corpuscles.

It is not improbable that the active process of phagocytosis, aside from the mechanical obstruction which the cells may cause, helps to determine the irregular distribution of the parasites in the body. At any rate it is certain that the parasites tend to accumulate in ordinary cases in the spleen and liver, the sites where the phagocytosis is most active. We have already pointed out, however, that the phagocytosis can be only one of many factors which influence the distribution.

There is a considerable amount of literature bearing upon the relation of phagocytosis to "natural resistance" and to "spontaneous cure" in malaria. It is a perfectly well ascertained fact that many patients suffering from malaria do, when placed under more favorable hygienic conditions, get entirely well without the administration of quinine or of any other drug. It is by no means uncommon to see patients begin to improve almost immediately after being put to bed in a hospital ward, the paroxysms becoming successively less severe, and the organisms gradually disappearing from the blood until all have vanished. What the natural mechanisms of defense are which lead to spontaneous cure, and which inhibit the growth and multiplication of many parasites even in the severer infections, it is as yet impossible to say definitely. All authorities are agreed that many of the progeny of segmenting organisms are disposed of at the end of each paroxysm, since did all the young ones gain entrance to red corpuscles and go on to full development, the blood would after a very few paroxysms show very few uninfected red globules, and those who hold that the blood serum kills off many of the small hyaline forms before they gain entrance to the interior of red corpuscles are not without grounds for their belief. Others maintain that the white corpuscles, the endothelial cells, and the spleen-pulp cells enclose many of the segments immediately, even before they have been deleteriously affected by the blood serum. The relative efficiency of the blood serum and of the phagocytes with relation to natural resistance, is being fought out on this as well as on other grounds. There can be little doubt (*vide* protocols) that many of the parasites taken up by the phagocytic cells are

enclosed within red corpuscles, and it may very well be that the alteration in the bodies of the red corpuscles may help to determine, especially in the spleen, their inclusion by white cells. That the re-reception of the parasites can do harm to the cells in many cases would seem to be evidenced by the fact that many of the makrophages are necrotic, their nuclei staining feebly or not at all in basic dyes, and their protoplasm showing an increased affinity for acid dyes like eosin. The diminution in the number of leucocytes after a paroxysm, however, is much more probably due to the effects of toxines set free at segmentation, and if so would be quite analogous to the similar diminution (leukolysis) which immediately follows the experimental injection of bacterial toxines into animals.

The changes which the parasites undergo within the bodies of the white cells are interesting to watch. It would appear that sometimes the parasite ruptures and that the pigment is gradually set free to be distributed in more or less regular lines throughout the protoplasm of the including cell. How long the parasites may live after inclusion appears doubtful. That they are taken up while alive seems certain from the many observations of skilled investigators. It is usually taken for granted that the phagocyte is the active agent and takes up the parasites, a much more likely view than that the parasites enter the white cells to feed on their deuteroplasm (fragmented or degenerated red corpuscles). It is not certain, however, that the parasites may not continue an intra-phagocytic existence at least for some time, especially if the protoplasm of the phagocyte is degenerated. Golgi has even gone so far as to suggest that the parasites may grow and multiply within certain of the body cells. Bignami cannot conceive of any explanation for the so-called "cases of latent infection" in malaria, that is, those instances in which an apparently cured malarial infection subsequently becomes active, without the patient having in the meantime been exposed to re-infection in a malarial district, except by assuming the continuance of some resistant forms inside of cells. Bignami argues that inasmuch as certain cells, leucocytes and endothelial cells for example, are known to take into themselves a certain number of sporulating forms, and further, since in patients with a recently cured malarial infection who have died from some intercurrent disease certain cells in the spleen, liver and bone marrow, retain the traces of infection, it is much more likely that the germs of latent

infection remain stored up in these cells than that they should exist for such a length of time free in the circulation. For if the parasite is capable of assuming some persistent form (crescentic or otherwise),[1] it is scarcely likely that such a form could long be retained inactive in the intercellular fluids, since it would almost certainly be taken up by phagocytes. Bastianelli and Bignami, however, combat Golgi's idea of the intra-cellular development of the parasites. There are many examples of latent bacterial infections, and the resistance of certain bacterial forms to the intra-cellular digestion is generally appreciated (cf. the researches of Wyssokowitch, Metschnikoff, *et al.*). For the present, however, it must be granted that we do not fully understand all the conditions which underlie latent infection.

Among the more interesting of the observations on phagocytosis in malaria are those dealing with the inclusion of certain phagocytes by other phagocytes—sometimes of phagocyte by phagocyte even to the third degree. As has been stated, the including cell sometimes looks necrotic, while in other instances it is the included cell which shows degenerative changes; occasionally both cells yield normal staining reactions. That such inclusions are not infrequent the sections from the fatal cases described in this report indisputably prove. Any attempt at explanation must be speculative. We can conceive of active small cells being attracted to the degenerating protoplasm of a large cell. This might explain the instances where the including cell looked degenerated. Or we can imagine the makrophage taking into its substance an enfeebled small phagocyte, in which case the included cell will be degenerated. Finally we can conceive of a small active phagocyte being attracted to a large, more sluggish phagocyte by the masses of food stuff (broken down red corpuscles, etc.) contained within the latter. A consideration at the present time of such cannibalistic and thieving tendencies on the part of the white cells would lead us too far afield, but such studies are among the many attractive problems connected with the sociology of cells, which, it is to be hoped, the physiologists will work out in the near future.

[1] As Bignami points out, it is evident that some explanation other than the resistance of crescents is necessary to account for the obstinacy of certain tertian and quartan infections.

DESCRIPTION OF PLATES.

PLATE III.

CASE C.—Liver—showing an accumulation of small round mononuclear cells in a portal space.

PLATE IV.

CASE C.—Liver—stained with haematoxylin and eosin—showing an area of necrosis with accumulation of leucocytes, many of which have distorted nuclei. Fine particles of malarial pigment may be seen within the endothelial cells of the capillaries and within some of the leucocytes.

Near the lower angle of the drawing a small thrombus containing numerous leucocytes is visible.

PLATE V.

CASE C.—Liver; haematoxylin and eosin; high power.

Fig. 1.—Hyaline thrombosis of an hepatic capillary; accumulation of leucocytes; nuclear distortion; a little malarial pigment present.

Fig. 2.—Thrombosis of adjacent capillaries; disappearance of intervening liver cells; leucocytic accumulation; distortion and fragmentation of nuclei.

PLATE VI.

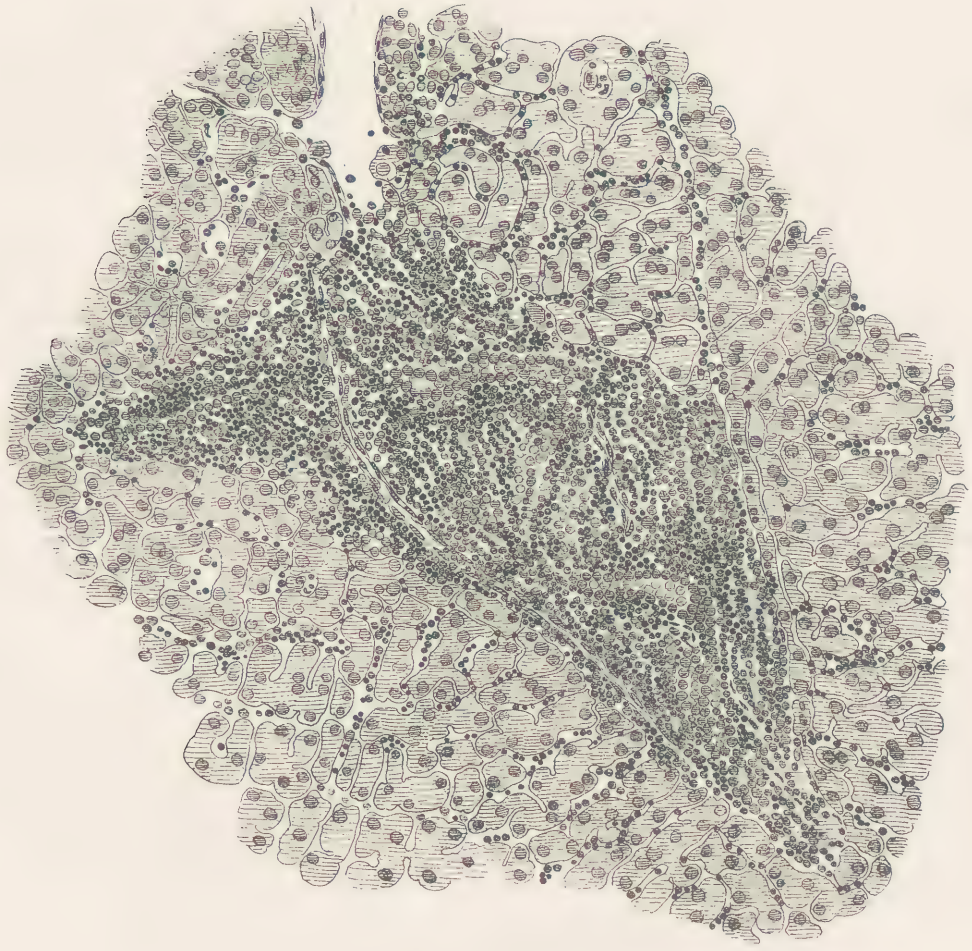
CASE D.—Spleen in mixed malarial and streptococcus infection. Tissue hardened in alcohol; section stained in methylene blue; accumulation of parasites and cocci within the vessels. Many of the malarial parasites have been absorbed by phagocytes. In the lower angle of the large vessel to the right a large mononuclear leucocyte is visible which contains four parasites. Occasionally cocci and malarial parasites are to be seen inside the same phagocyte.

The makrophages in the splenic pulp, some containing coarse clumps, others finer particles of malarial pigment, are numerous.

Inside the vessels the makrophages are quite like those described within the hepatic capillaries of this case.

Some of the endothelial cells contain malarial pigment within their protoplasm.

A blue-stained non-pigmented sphere within the malarial parasite is well shown in several parts of the drawing.



Lith. Anst. v. E. A. Funke, Leipzig

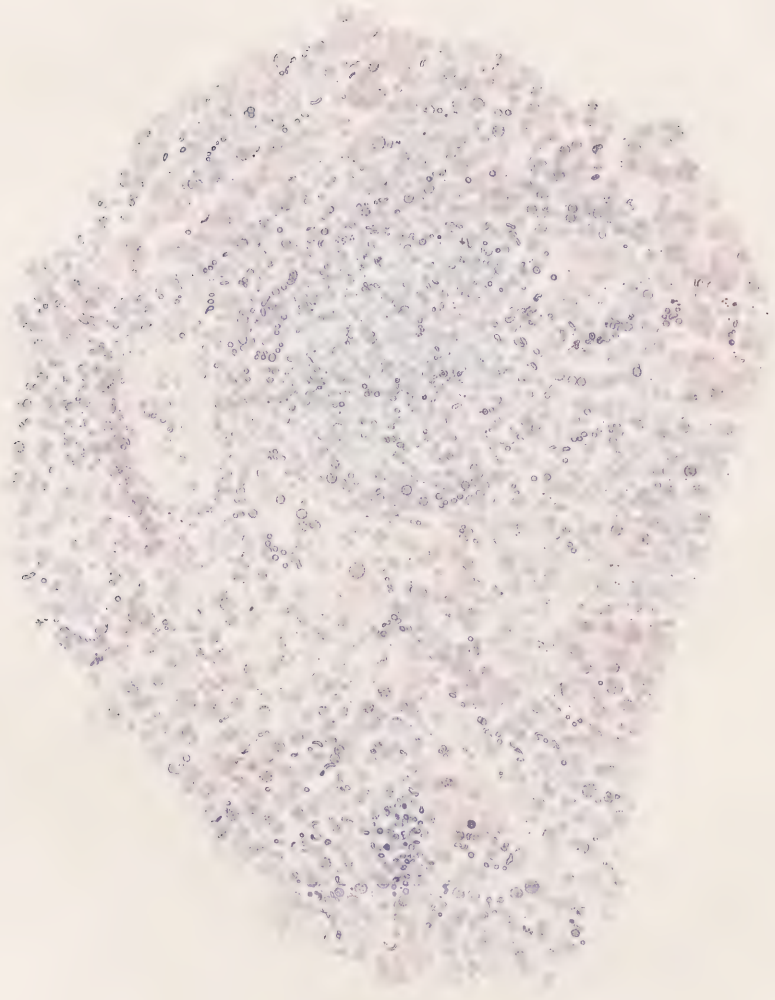


Fig. 1.

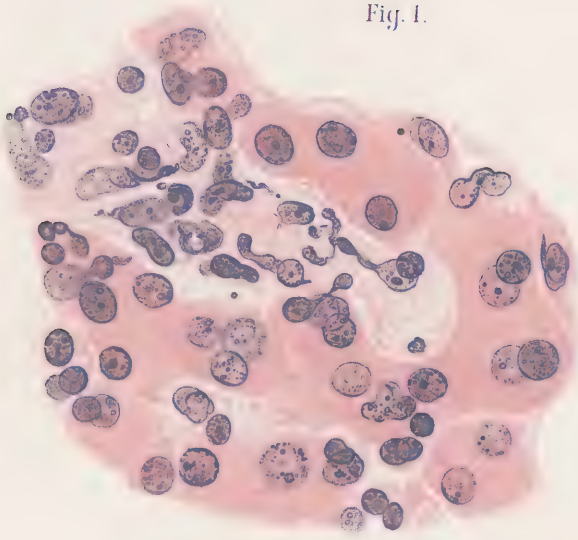
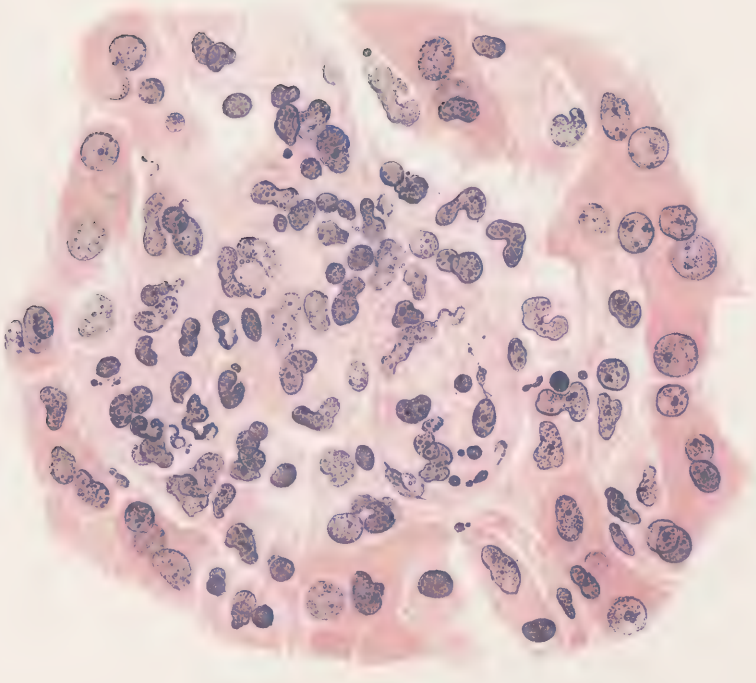
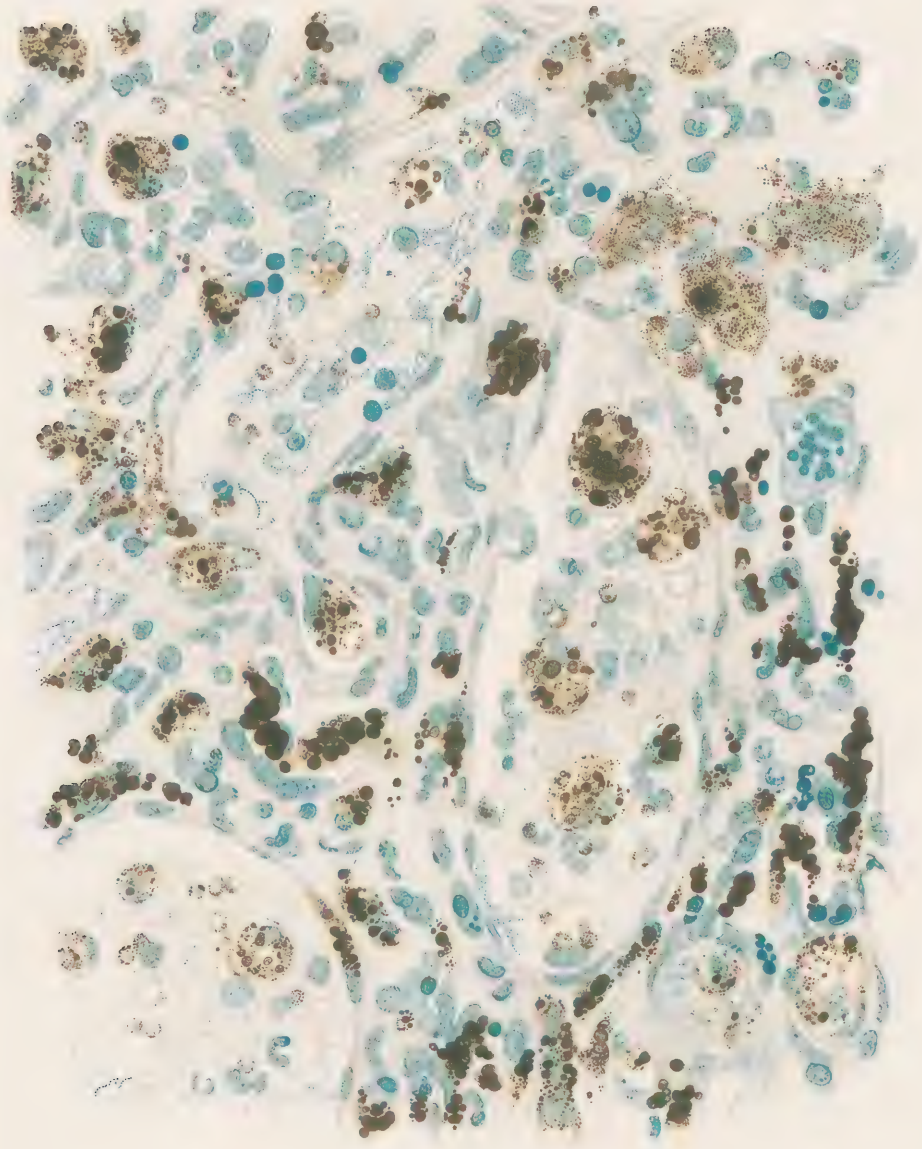


Fig. 2.



M. Brödel Del. Lith. Anst. v. E. A. Funke Leipzig.



N. Lovell, Del. E.A. Funke, Lith.

Publications of the Johns Hopkins Hospital.

THE JOHNS HOPKINS HOSPITAL REPORTS.

Volume I. This volume is now in press. It will contain the studies from the Pathological Laboratory. It will be edited by Dr. W. H. Welch, Professor of Pathology and Pathologist to the Hospital.

Volume II. This volume is complete. It includes 570 pages and 28 plates and figures. It will be furnished, bound in cloth, for $5.00.

Its contents are as follows:

MEDICAL REPORT FOR 1890, *I. Price* 50 *Cents.*

I. On Fever of Hepatic Origin, particularly the Intermittent Pyrexia associated with Gallstones. By WILLIAM OSLER, M. D.
II. Some Remarks on Anomalies of the Uvula, with special reference to Double Uvula. By JOHN N. MACKENZIE, M. D.
III. On Pyrodin. By H. A. LAFLEUR, M. D.
IV. Cases of Post-febrile Insanity. By WILLIAM OSLER, M. D.
V. Acute Tuberculosis in an Infant of Four Months. By HARRY TOULMIN, M. D.
VI. Rare Forms of Cardiac Thrombi. By WILLIAM OSLER, M. D.

MEDICAL REPORT FOR 1890, *II.*

VII. Notes on Endocarditis in Phthisis. By WILLIAM OSLER, M. D.
VIII. Tubercular Peritonitis. By WILLIAM OSLER, M. D.
IX. A Case of Raynaud's Disease. By H. M. THOMAS, M. D.
X. Acute Nephritis in Typhoid Fever. By WILLIAM OSLER, M. D.

REPORT IN GYNECOLOGY, I.

XI. The Gynecological Operating Room and the Antiseptic and Aseptic Rules in Force. By HOWARD A. KELLY, M. D.
XII. The Laparotomies performed from October 16, 1889, to March 3, 1890. By HOWARD A. KELLY, M. D., and HUNTER ROBB, M. D.
XIII. The Report of the Autopsies in Two Cases Dying in the Gynecological Wards without Operation. By HOWARD A. KELLY, M. D.
XIV. Composite Temperature and Pulse Charts of Forty Cases of Abdominal Section. By HOWARD A. KELLY, M. D.
XV. The Management of the Drainage Tube in Abdominal Surgery. By HUNTER ROBB, M. D.
XVI. The Gonococcus in Pyosalpinx. By HOWARD A. KELLY, M. D.
XVII. Tuberculosis of the Fallopian Tubes and Peritoneum. Ovarian Tumor. By HOWARD A. KELLY, M. D.
XVIII. General Gynecological Operations from October 15, 1889, to March 4, 1890. By HOWARD A. KELLY, M. D.
XIX. Report of the Urinary Examination of Ninety-one Gynecological Cases. By HOWARD A. KELLY, M. D., and ALBERT A. GHRISKEY, M. D.
XX. Ligature of the Trunks of the Uterine and Ovarian Arteries as a Means of Checking Hemorrhage from the Uterus, etc. By HOWARD A. KELLY, M. D.
XXI. Carcinoma of the Cervix Uteri in the Negress. By J. WHITRIDGE WILLIAMS, M. D.
XXII. Elephantiasis of the Clitoris. By HOWARD A. KELLY, M. D.
XXIII. Myxo-Sarcoma of the Clitoris. By HUNTER ROBB, M. D.
XXIV. Kolpo-Ureterotomy. Incision of the Ureter through the Vagina, for the treatment of Ureteral Stricture. By HOWARD A. KELLY, M. D.
XXV. Record of Deaths following Gynecological Operations. By HOWARD A. KELLY, M. D.

REPORT IN SURGERY, I.

XXVI. The Treatment of Wounds with Especial Reference to the Value of the Blood Clot in the Management of Dead Spaces. By WILLIAM S. HALSTED, M. D.

REPORT IN NEUROLOGY, I. Price 50 *Cents.*

XXVII. A Case of Chorea Insaniens, with a Contribution to the Germ Theory of Chorea. By HENRY J. BERKLEY, M. D.
XXVIII. Acute Angio-Neurotic Oedema. By CHARLES E. SIMON, M. D.
XXIX. Haematomyelia. By AUGUST HOCH, M. D.
XXX. A Case of Cerebro-Spinal Syphilis, with an unusual Lesion in the Spinal Cord. By HENRY M. THOMAS, M. D.

REPORT IN PATHOLOGY, I.

XXXI. Amœbic Dysentery. By WILLIAM T. COUNCILMAN, M. D., and HENRI A. LAFLEUR, M. D.

Part I (containing the first four papers named above) and Part VI, *Report in Neurology* (containing the papers numbered XXVII–XXX, inclusive, above) can still be furnished separately. The other papers can be furnished only in the complete bound volume.

Volume III is complete. It includes 766 pages and 69 plates and figures. It will be furnished, bound in cloth, for $5.00.

Its contents are as follows:

REPORT IN PATHOLOGY, II. Price $2.00.

I. Papillomatous Tumors of the Ovary. By J. WHITRIDGE WILLIAMS, M. D. With two plates.
II. Tuberculosis of the Female Generative Organs. By J. WHITRIDGE WILLIAMS, M. D.

[OVER]

REPORT IN PATHOLOGY, III. Price $2.00.

III. Multiple Lympho-Sarcomata, with a report of Two Cases. By Simon Flexner, M. D. With two plates.
IV. The Cerebellar Cortex of the Dog. By Henry J. Berkley, M. D. With one plate.
V. A Case of Chronic Nephritis in a Cow. By W. T. Councilman, M. D. With one plate.
VI. Bacteria in their Relation to Vegetable Tissue. By H. L. Russell, Ph. D.
VII. Heart Hypertrophy. By Wm. T. Howard, Jr., M. D.

REPORT IN GYNECOLOGY, II. Price $3.00.

VIII. The Gynecological Operating Room. With two plates.
IX. An External Direct Method of Measuring the Conjugata Vera. By Howard A. Kelly, M. D. With three plates.
X. Prolapsus Uteri without Vesical Diverticulum and with Anterior Enterocele. By Howard A. Kelly, M. D. With five figures.
XI. Lipoma of the Labium Majus. By Howard A. Kelly, M. D.
XII. Deviations of the Rectum and Sigmoid Flexure associated with Constipation a Source of Error in Gynecological Diagnosis. By Howard A. Kelly, M. D. With one plate and fifteen figures.
XIII. Operations for the Suspension of the Retroflexed Uterus. By Howard A. Kelly, M. D. With four plates.
XIV. Potassium Permanganate and Oxalic Acid as Germicides against the Pyogenic Cocci. By Mary Sherwood, M. D.
XV. Intestinal Worms as a Complication in Abdominal Surgery. By Albert L. Stavely, M. D.
XVI. Gynecological Operations not involving Cœliotomy. By Howard A. Kelly, M. D. Tabulated by A. L. Stavely, M. D.
XVII. The Employment of an Artificial Retroposition of the Uterus in covering Extensive Denuded Areas about the Pelvic Floor. By Howard A. Kelly, M. D. With seven figures.
XVIII. Some Sources of Hemorrhage in Abdominal Pelvic Operations. By Howard A. Kelly, M. D. With five figures.
XIX. Photography Applied to Surgery. By A. S. Murray. With five plates.
XX. Traumatic Atresia of the Vagina with Hæmatokolpos and Hæmatometra. By Howard A. Kelly, M. D. With four plates and two figures.
XXI. Urinalysis in Gynecology. By W. W. Russell, M. D.
XXII. The Importance of employing Anæsthesia in the Diagnosis of Intra-Pelvic Gynecological Conditions. Demonstrated by an Analysis of 240 Cases. By Hunter Robb, M. D. With eight plates.
XXIII. Resuscitation in Chloroform Asphyxia. By Howard A. Kelly, M. D. With two plates.
XXIV. One Hundred Cases of Ovariotomy performed on Women over Seventy Years of Age. By Howard A. Kelly, M. D., and Mary Sherwood, M. D.
XXV. Abdominal Operations performed in the Gynecological Department, from March 5, 1890, to December 17, 1892. By Howard A. Kelly, M. D.
XXVI. Record of Deaths occurring in the Gynecological Department from June 6, 1890, to May 4, 1892.

Volume IV contains the following Reports. Subscription $5.00.

REPORT ON TYPHOID FEVER. By Wm. Osler, M. D. $1.00.
REPORT IN NEUROLOGY, II. By H. J. Berkley, M. D. $1.50.
REPORT IN SURGERY, II. By W. S. Halsted, M. D. $1.00.
REPORT IN GYNECOLOGY, III. By Thomas S. Cullen, M. B. $1.00.
REPORT IN PATHOLOGY, IV. By J. Whitridge Williams, M. D. (now in press, completing the volume). $0.75.

Volume V is now in progress. Subscription $5.00. The following are issued.

THE MALARIAL FEVERS OF BALTIMORE. By W. S. Thayer, M. D., and J. Hewetson, M. D. $2.00.
A STUDY OF SOME FATAL CASES OF MALARIA. By Lewellys F. Barker, M. B. $0.75.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains announcements of courses of lectures, programmes of clinical and pathological study, details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. Nine numbers will be issued annually. The subscription price is $1 00 per year. Volume VI is now in progress.

Volumes I, II, III, bound together in cloth. Price $5.00. Volume IV, in cloth. Price, $1.00. Volume V, in cloth. Price, $1.00.

DESCRIPTION OF THE JOHNS HOPKINS HOSPITAL.

By John S. Billings, M. D., LL. D.

Containing 56 large quarto plates, phototypes, and lithographs, with views, plans and detail drawings of all the buildings, and their interior arrangements—also wood-cuts of apparatus and fixtures; also 116 pages of letter-press describing the plans followed in the construction, and giving full details of heating-apparatus, ventilation, sewerage and plumbing. Price, bound in cloth, $7.50.

HOSPITAL PLANS.

Five essays relating to the construction, organization, and management of Hospitals, contributed by their authors for the use of the Johns Hopkins Hospital.

These essays were written by Drs. John S. Billings of the U. S. Army, Norton Folsom of Boston, Joseph Jones of New Orleans, Caspar Morris of Philadelphia, and Stephen Smith of New York. They were originally published in 1875. Price, bound in cloth, $5.00.

Subscriptions for the above publications may be sent to

The Johns Hopkins Press, Baltimore, Md.